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PRESENT CONCEPTS IN INTERNAL MEDICINE

MAJ John J. Jolley, MC, Nina Z. Sanders, B.A., and Cathleen E. Swee, B.A.

Letterman Army Medical Center
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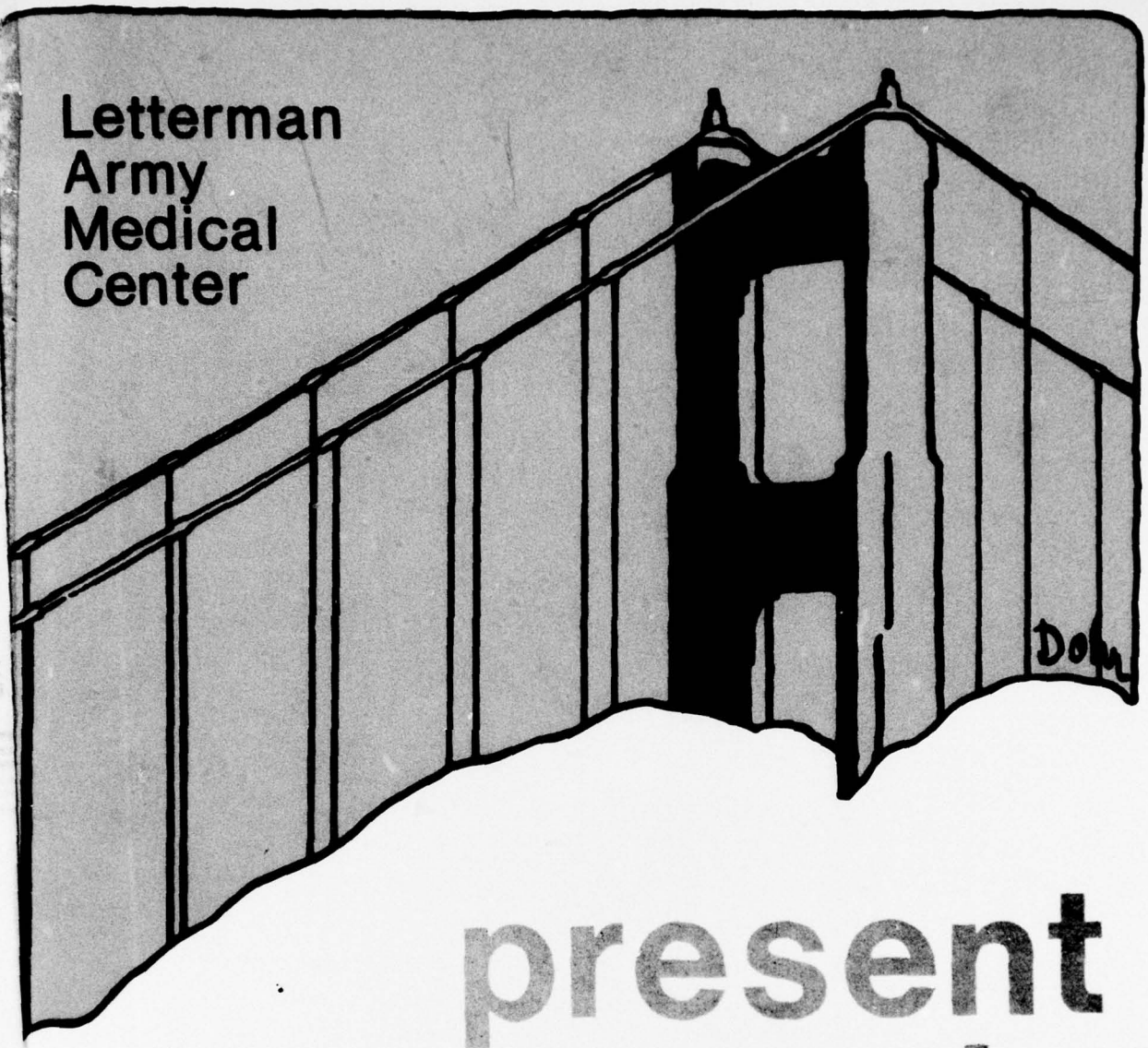

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This symposium consists of six articles , five appendices, four figures, and one table (for quick reference). It includes articles on fluid and electrolyte disorders in cirrhosis; hepatic encephalopathy syndrome; coagulation abnormalities in liver disease; fulminant hepatic failure; variceal hemorrhage; and congenital hepatic fibrosis with sepsis and hypersplenism. Appendices include: 2 (cont on p 3)

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PRESENT CONCEPTS

IN INTERNAL MEDICINE

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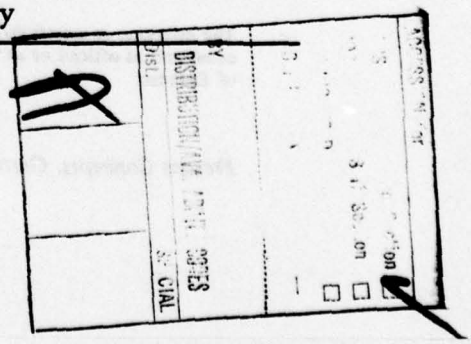

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Present Concepts, Gastroenterology Symposium, Fall 1977

PRESENT CONCEPTS IN INTERNAL MEDICINE

Gastroenterology Symposium, Fall 1977

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FOREWORD

This Symposium reflects the common problems facing the general internist when dealing with severe liver disease. We have selected the nonsurgical, life-threatening clinical situations in hepatology and have attempted to describe the pathophysiologic bases for current therapy. Unfortunately, much of the physiology in liver disease remains to be elucidated, so that most of our therapy is empiric, nonspecific, and supportive.

You will find therapeutic guidelines in the Appendix; these are meant to stimulate your memory more than to serve as specific cookbook guides.

JOHN J. JOLLEY, M.D.
Major, MC
Assistant Chief, Gastroenterology Service
Guest Editor

The more questionable the indications for requesting a laboratory test, the greater the problems the answer will cause.

●●●●●●●●●●●

Osler's Rules:

1. *First of all, do no harm.*
2. *If you are confused, examine the patient; do not rely on indirect observations.*
3. *If you want a task done well, do it yourself.*
4. *Successful medical care requires the physician give his patient respect, dignity, and concern.*

●●●●●●●●●●●

If everything seems to be going well, you have overlooked something.

FLUID AND ELECTROLYTE DISORDERS IN CIRRHOSIS

Lieutenant Colonel David C. Staples, MC

Although much has been written about ascites and the hepatorenal syndrome as separate entities, little attempt has been made to point out that they represent different stages in the disordered fluid and electrolyte metabolism of patients with cirrhosis and, as such, share pathophysiologic mechanisms. The purpose of this paper is to discuss the pathophysiology and treatment of the fluid and electrolyte abnormalities that accompany cirrhosis.

PATHOPHYSIOLOGY OF ASCITES

Ascites is a localized collection of extracellular fluid in the peritoneal cavity. Localization of the fluid collection depends on intraabdominal factors, but its formation depends on both local and systemic factors. Starling's hypothesis states that movement of fluid between the vascular and interstitial fluid compartments is regulated by the balance of hydrostatic and oncotic forces across the capillary wall. The major intraabdominal factors determining the formation of ascitic fluid are the serum oncotic pressure, portal capillary pressure, and lymphatic drainage. In addition, systemic renal factors regulating sodium excretion contribute to its formation. The contribution of each of these factors will be considered separately.

The major determinant of serum oncotic pressure is the serum albumin concentration. Although the rate of albumin synthesis is usually reduced in cirrhosis /1,2/, this reduction is compensated for by diminished degradation /3/. The low serum albumin concentration may be secondary to the increased plasma volume which occurs in these patients. /4/ The decreased albumin concentration is not the only determinant of ascitic fluid formation because there is poor correlation between its concentration and the presence or absence of ascites in patients with cirrhosis. /5,6/ In addition, since the capillaries of the digestive tract are highly permeable to plasma protein, decreased serum oncotic pressure

opposes ascitic fluid accumulation. /5/ Finally, albumin infusions given over a period of several months have no effect on life expectancy, working capacity, control of fluid retention, or drug requirement in patients with resistant ascites, provided aldosterone antagonists, thiazides, and sodium restriction are employed. /7/

Portal capillary pressure is another major determinant for ascitic fluid accumulation /8/ as evidenced by the fact that accumulation of ascites is accelerated when cirrhosis is complicated by portal vein obstruction /5,9/ and that refractory ascites is usually controlled by portacaval anastomosis /1,2,5,8,10/, a procedure which reduces portal pressure. That this is not the only determinant is evidenced by the fact that experimental obstruction of the portal vein results in an acute rise in extrahepatic portal pressure, but pressure is not sustained and ascites does not occur unless the animal is also made hypoalbuminemic. /5,11/ In addition, there is little correlation between the portal pressure and the presence of ascites. /5/ Cirrhosis not only causes presinusoidal, but also postsinusoidal portal hypertension, as evidenced by three-dimensional studies and wax model reconstructions of cirrhotic livers, which demonstrate flattening and circumscribed narrowing of the hepatic veins by extrinsic pressure from regenerative nodules. /2/ Cinefluorographic studies performed at the time of hepatic vein catheterization confirm this finding. /2/ That postsinusoidal block may cause ascites has been amply demonstrated by hepatic vein occlusion studies in dogs. /2,5,9,11/ It probably plays a minor role in ascitic formation of cirrhosis in man, however, since there is no correlation between the decrease in central and hepatic veins in cirrhotic patients and the presence of ascites. /2,12/ In addition, there is no correlation between the degree of hepatic scarring and the presence of ascites. /2,13/ Other evidence against a major role for postsinusoidal block is the protein concentration of the ascitic fluid which has the character of a transudate in cirrhosis but that of an exudate in hepatic vein occlusion. /5,9,11/ Finally, remission of ascites is equally effective with end-to-side portacaval anastomosis as with side-to-side anastomosis. /1,2,5,8,10/ This should not be the case if the primary origin of the ascitic fluid was postsinusoidal block.

Since the formation of edema fluid implies lymph formation in excess of drainage, impaired lymphatic drainage or excess formation have been postulated to be etiologic factors in ascitic fluid formation. This assumption is supported by the fact that increased flow of thoracic duct lymph is a hallmark of cirrhosis whether or not ascites is present. /2,5,14/ Against this hypothesis is the fact that there is no correlation of thoracic duct lymph flow with the presence or absence of ascites /5/ and the fact that refractory ascites can be treated effectively by end-to-side portacaval anastomosis /1,2,5,8,10/, a procedure which would not improve lymph drainage.

Renal factors regulating sodium absorption and free water clearance also contribute significantly to the formation of ascites. An evaluation of the pathophysiology of the "hepatorenal syndrome" provides insight concerning these renal factors.

PATHOPHYSIOLOGY OF THE HEPATORENAL SYNDROME

Although the term "hepatorenal syndrome" has been used loosely to describe any condition which involves both organs simultaneously /15/, it should be applied only to the *acquired functional* renal failure which occurs in cirrhotic patients with end stage liver disease. The definition implies that there are no morphologic changes in the kidneys. /15-19/ The fact that these kidneys function normally if transplanted bears this out. /20/

Certain clinical and biochemical features characterize the disorder. Clinically, the patient with hepatorenal syndrome has severe ascites and oliguria. /21/ There is good correlation between the degree of hepatic dysfunction and renal dysfunction. /21/ Patients with hepatorenal syndrome rarely recover; when they do, their recovery is related to improvement in hepatic function. /22/ Ascites is invariably a finding in these patients, and the presence of refractory ascites usually precedes the onset of the syndrome. Oliguria is also an invariable finding. The maximal urinary flow rate correlates with the rate of glomerular filtration and the rate of solute excretion, but not with the rate of sodium excretion.

This correlation could be explained if the patients with normal flow rates and decreased sodium excretion reabsorbed sodium distally and those with decreased flow rates reabsorbed it proximally. /23/ The biochemical features of hepatorenal syndrome /22/ include hyponatremia secondary to impaired free water clearance; progressive azotemia with blood urea nitrogen (BUN) out of proportion to creatinine; urinary specific gravity greater than 1.01, probably secondary to increased antidiuretic hormone (ADH); and urinary sodium excretion of less than 10 millequivalents per liter per day.

The pathophysiology of the hepatorenal syndrome has been evaluated revealing two basic problems: decreased sodium excretion, and impaired water diuresis. The decreased sodium excretion is secondary both to decreased filtration and to increased reabsorption. Inulin clearance in cirrhosis without ascites is normal, whereas in patients with resistant ascites, it is below normal. It is decreased even further in patients with azotemia. /21/ This, coupled with the fact that the hepatorenal syndrome frequently follows gastrointestinal hemorrhage, diuresis, or paracentesis, has led to the assumption that the plasma volume is decreased in this condition. Plasma volume, in fact, is *increased* in cirrhosis, with or without ascites or hepatorenal syndrome. /4/ In addition, there is no correlation between the percentage of reabsorption of sodium and the glomerular filtration rate /20/. This has led to the postulate that the "effective plasma volume" is diminished in this disorder.

Attempts to test this hypothesis with volume expansion show conflicting results. Tristani and Cohn /24/, in studying the effects of volume expansion on the systemic and renal hemodynamics of 21 patients with cirrhosis, ascites, and oliguria, noted two subgroups of patients. The patients in Group 1 had low blood volume, low or normal cardiac index, and elevated renal vascular resistance. Patients in Group 2 had increased or normal blood volume, increased cardiac index, and increased renal vascular resistance (but lower than those in Group 1). Nearly all patients had decreased renal blood flow, increased renal vascular resistance, and decreased renal fraction of cardiac output. After volume expansion, systemic vascular resistance fell (18/21) and renal vascular resistance decreased (13/14). Cardiac index increased (19/21)

as did renal blood flow (12/14) and renal fraction of cardiac output. The changes were greatest in Group 1, suggesting that even a normal cardiac output may be relatively low in cirrhosis because of associated atrioventricular shunting. Blood volume and cardiac output in Group 1 patients is contradictory to other studies done on similar patients /25/, and suggests volume depletion in this subset. McCloy et al /26/ evaluated 22 patients with cirrhosis, the majority of whom had ascites and a third of whom had azotemia. They evaluated the effects of albumin and saline infusions and found that single infusions of 50 grams of albumin produced plasma volume expansion and a mean increase in effective renal plasma flow, but not in glomerular filtration rate. No correlation existed between changes in plasma volume and effective renal plasma flow. Increases in effective renal plasma flow were limited to patients with normal or only modestly impaired renal function, whereas those patients with the worst renal function did not respond. Repeated albumin infusions did not alter the glomerular infiltration rate or effective renal plasma flow, although the plasma volume was expanded and serum albumin concentrations were raised. Hypertonic saline infusions produced an increase in plasma osmolality but did not affect the glomerular filtration rate or the effective renal plasma flow. Urinary excretion of water and electrolytes was not significantly affected by infusions of either albumin or saline. Lieberman et al /27/ also provide indirect evidence that challenges the hypothesis of a decreased effective plasma volume in this disorder.

Increased sodium reabsorption occurs in both the proximal /28/ and the distal /29-31/ tubule in hepatorenal syndrome. Schedel and Bartter /28/ postulated that the decreased free water clearance sometimes seen in cirrhosis is secondary to increased proximal tubule reabsorption with less sodium available for reabsorption distally and subsequent generation of free water clearance. As evidence, they demonstrated that mannitol infusion increases free water excretion in patients with cirrhosis. Distal tubular reabsorption of sodium secondary to hyperaldosteronism also occurs in cirrhosis with ascites and probably explains the lack of correlation of urinary flow rate and sodium excretion in this disorder. The hyperaldosteronism is secondary to diminished degradation as well as to increased production. /29/ The importance of hyperaldosteronism is verified by the response of patients with cirrhosis and ascites to aldosterone suppression. /30,31/

A probable explanation for the increased sodium reabsorption is the alteration in intrarenal distribution of blood flow. Epstein et al /17/, by use of 133 Xenon washout studies, demonstrated vasoconstriction with redistribution of blood flow away from the cortical area, namely corticomedullary shunting, in this disorder. That these changes are functional was established by the fact that they are variable and unstable, and by the comparison of premortal and postmortem arteriograms. The changes are also found in compensated nonazotemic patients with cirrhosis, again suggesting that it is etiologically important. /32/ An excellent correlation existed between the degree of corticomedullary shunting and the magnitude of renal functional impairment as measured by the creatinine clearance. /17/ This fits well with the fact that the kidneys in the hepatorenal syndrome function as if the glomerular filtration rate was reduced but tubular function maintained. Shunting of blood flow from the cortical area with preservation of flow to the juxtamedullary nephrons also explains the avid sodium retention.

Hepatorenal syndrome is further characterized by a diminished free water clearance which decreases steadily from patients with ascites to refractory ascites and finally to hepatorenal syndrome. /21/ Evidence suggests that this decrease is secondary to increased proximal tubular reabsorption of sodium as mentioned above /28/, although it does not explain the oliguria and urine which are hyperosmolor relative to plasma. Rather, these findings, along with early indirect assay methods /33/, suggest ADH effect. Padfield and Morton /34/ measured arginine vasopressin by radioimmunoassay in 10 patients with cirrhosis, four of whom had ascites, and found the levels to be widely distributed, with elevation present in only five patients. There was no tendency for those patients with ascites to have higher levels and there was no association between ADH levels and hyponotremia. DeTroyer et al /35/ administered demeclocycline to five patients with cirrhosis with refractory ascites. This agent, a tetracycline derivative that has been shown to inhibit tubular action of ADH, resulted in excretion of hyperosmolar urine, water diuresis, and weight loss. However, renal impairment possibly caused by hypovolemia, the antianabolic effect of the drug, or drug-induced nephrotoxicity, occurred in four of these patients. Thus, the role of ADH in this condition remains unclear.

The pathogenesis of hepatorenal syndrome remains speculative but may be accounted for either by increased renal sympathetic tone or by a humoral vasoactive substance. /15/ Schroeder et al /25/ demonstrated that in cirrhosis with ascites, plasma renin concentrations are high and concentrations of renin substrate, produced by the liver, are low. There is a significant difference between mean renin levels in patients with normal renal function and patients with renal failure. In addition, a significant correlation exists between plasma renin and renal function as estimated by the glomerular infiltration rate. There is no correlation between cardiac output or plasma volume and plasma renin. However, augmentation of renal plasma flow with dopamine is accompanied by a decrease in plasma renin, suggesting that the increased renin is secondary to decreased renal plasma flow. /36/ Finally, isolated dog kidney perfusion experiments demonstrate that renal cortical flow *decreases* with depletion of renin substrate in the profusate and *increases* with the addition of renin substrate to the depleted perfusate. /19/ Recovery from this syndrome following infusion of plasma containing high levels of renin substrate has been reported by the same authors. /37/

TREATMENT OF ASCITES

Since the major problem in most edematous conditions is the retention of sodium, the major therapy for ascites is sodium restriction, with or without diuretic therapy. /1,38,39/ Sherlock /40/ recommends restriction to a 500 milligram (mg) per day sodium intake, since the daily urinary excretion is less than 200 mg and extrarenal losses are not greater than 500 mg. Intake of over 750 mg per day of sodium results in positive sodium balance and development of ascites, or worsening of it. Fluid restriction is usually unnecessary unless the patient is hyponatremic (usually a reflection of impaired water diuresis); then, restriction of fluids to 1,500 milliliters (ml) per day may be necessary. If after four days of bedrest and sodium restriction the patient fails to lose two kilograms, diuretics should be added. My personal preference is spironolactone (Aldactone®), 100 mg per day, in four divided doses. Most patients respond to this dosage, although about one-third of them may require as much as 300 mg per day. Aldactone may be used alone or in combination with a

diuretic such as thiazide which acts more proximally. Such combination has greater rationale than thiazide diuretics alone, since the sodium blocked from proximal reabsorption is readily absorbed distally. In addition, it prevents hypokalemia in patients who already have low total body potassium stores. /39/ Although ascites in the vast majority of patients can be controlled with these measures, complications occur in up to 75% of patients /41/, especially in those patients treated with more potent diuretics, such as furosemide (Lasix®), and ethacrynic acid (Edecrin®). Complications, including hypokalemia, hyponatremia, azotemia, hypochloremic alkalosis, and hepatic encephalopathy, can be minimized by following certain guidelines. /3/ First, diuretics should be withheld until major disorders of electrolyte balance have been corrected. Second, they should be employed with extreme caution in patients prone to encephalopathy, or in patients with hyponatremia or severe impairment of renal function. Finally, they should never be prescribed for patients with hepatic encephalopathy or azotemia caused by renal circulatory failure. It is important to keep in mind that ascitic fluid is in dynamic equilibrium with other body fluids. /42-44/ Guidelines for the magnitude of diuresis which safely avoid hypovolemia have been provided by Sheer et al /45/, who demonstrated that transperitoneal absorption of ascitic fluid cannot exceed one liter for 24 hours in patients with peripheral edema and may be as little as 300 ml in patients without peripheral edema.

Other methods for treating ascites offer few or no advantages in addition to those described above, but are included for the sake of completeness. The first methods to be discussed are those designed to improve intraabdominal factors facilitating formation of ascites. Wilkinson and Sherlock /7/ in 1962 demonstrated that repeated albumin infusions have no effect on life expectancy, working capacity, control of fluid retention, or drug requirement in patients with resistant ascites, provided aldosterone antagonists, thiazides, and sodium restrictions are employed. From 275 to 675 grams of albumin are required to return serum albumin to normal, and 12.5 to 100 grams weekly are required to maintain it. Even if the technique were effective, the cost would be prohibitive. Other measures aimed at treating the underlying abdominal factors include cannulation of the thoracic duct to improve lymph drainage, and portacaval anastomosis to reduce portal pressure. Cannulation of the

thoracic duct /14/ does not relieve ascites if colloid and electrolyte losses from this drainage procedure are replaced. Although Crane /10/ established that portacaval shunts are effective in treating ascites, the mortality rate in patients with refractory sites is up to 50% and hepatic encephalopathy frequently is a side effect.

One final technique which merits consideration is that of paracentesis with reinfusion of ascitic fluid. /46-49/ Vlahcevic et al /47/ demonstrated that intravenous infusion of ascitic fluid or albumin and saline during and after paracentesis resulted in moderate diuresis and natruresis similar to that produced by diuretic therapy alone. There was no significant difference between ascites reinfusion and albumin and saline replacement of discarded ascitic fluid. However, the combination of diuretics (spironolactone and thiazides) and intravenous replacement therapy during paracentesis resulted in marked diuresis and natruresis, a better result than attained by either method alone. In a long-term comparison, however, the combination therapy failed to improve patient survival or prevent fatal renal failure. /48/ Eknoyan et al /49/ demonstrated that ascitic fluid reinfusions plus furosemide had beneficial effects over either therapy alone. Ascitic fluid reinfusion alone resulted in increased glomerular filtration rate, renal plasma flow, and potassium excretion without change in sodium excretion or urinary volume, while furosemide alone resulted in increased sodium and potassium excretion and urine volume. The combination of both resulted in increased glomerular infiltration rate, renal plasma flow, sodium and potassium excretion, and urine volume with no deterioration in renal function. Surgical application of this principle has led to construction of peritoneal-jugular shunts with encouraging preliminary results, but appropriate controls are lacking. /50/ See page A-1, Appendix A, for Treatment Summary for therapy of ascites secondary to liver disease.

TREATMENT OF THE HEPATORENAL SYNDROME

Treatment of the functional renal failure of cirrhosis is more difficult and depends primarily upon supportive therapy and attempts to improve hepatic function. It depends, in fact, upon improvement in hepatic function /22/ as evidenced by resolution following hepatic transplantation. /19/

Volume expansion has been attempted because of the postulated decreased "effective plasma volume" and results have been conflicting, as discussed previously. /24,26,27/ The major benefit of volume expansion is to eliminate the possibility of prerenal azotemia, a condition which may mimic the biochemical features of this disorder. For this reason, I believe that all patients considered to have the hepatorenal syndrome should have a cautious trial of volume expansion. Hemodynamic studies done during paracentesis in patients with tense ascites suggest that this may be beneficial. /51/ Removal of less than 1,500 ml of fluid resulted in increased cardiac output and stroke volume and decreased peripheral vascular resistance. Gordon /52/ reported that rapid paracentesis of eight to 19 liters resulted in decreased inferior vena cava and renal vein pressures, increased glomerular filtration rate and effective renal plasma flow, and increased sodium excretion. Changes in urinary flow rate were unpredictable. The combination of paracentesis and ascitic fluid reinfusion referred to previously /46-49/ might be beneficial, although such therapy in patients with refractory ascites neither prolonged survival nor prevented renal failure. /10/

Because of the renal circulatory changes described in this disorder, various vasoactive amines have been tried but have met with little success. Metaraminol (Aramine®) results in a transient increase in urinary output but has no effect on glomerular filtration rate and renal plasma flow when administered for a short term. /21/ When used long term in combination with plasma volume expansion /53/, it results in increased peripheral vascular resistance, decreased cardiac output, and increased sodium excretion but does not improve mental status or increase survival. Dopamine, in pressor or subpressor doses, increases cardiac output, renal blood flow, and glomerular filtration rate, and decreases renal vascular resistance. /54/ Because of these properties, it has been tried in the hepatorenal syndrome. When administered in subpressor doses, it results in increased renal plasma flow without increased glomerular filtration rate, urinary output, or sodium excretion. /54/ The most promising agent seems to be Octapressin, a synthetic analog of vasopressin, which produces systemic vasoconstriction associated with an increase in renal blood flow. Cohn et al /18/, reported an increase in arterial pressure and a striking solute

diuresis when administered to three patients with hepatorenal syndrome. Kew et al /55/ felt this may have been secondary to an increase in the blood pressure. They found that administration of subpressor doses of this agent to patients with compensated cirrhosis resulted in increased renal blood flow in only one of six patients who had no increase in renal arterial pressure. Renal blood flow increased, however, in three of five patients in whom a rise in mean arterial pressure of five or more millimeters of mercury was produced. Concomitant with this improvement of renal blood flow was an increase in cortical perfusion using the 133 Xenon washout technique.

For Treatment Summary of the hepatorenal syndrome, please refer to page A-2, Appendix A.

****

If you cannot figure out a patient's problem, perhaps someone else can.

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Law of Medical Hysteria. Inappropriate medical activity is directly proportional to the gravity of the patient's illness and inversely proportional to the likelihood of real or lasting therapeutic benefit.

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Murphy's Laws:

A. If it is absolutely impossible for anything to go wrong, it will anyway. Trying to correct it will only make matters worse.

B. If anything can go wrong, it will.

C. When anything goes wrong, it does so all at once.

D. Any error that can creep in, will. It will always be in the direction that will do the most harm.

E. When left to themselves, things go from bad to worse.

F. If two things can go wrong, the worst one will happen.

G. If something goes wrong, it will be at the most inconvenient time.

●●●●●●●●●●●

Eric's Dictum: No guts, no glory.

Present Concepts, Gastroenterology Symposium, Fall 1977

HEPATIC ENCEPHALOPATHY SYNDROME

Major John A. Dale, MC

DEFINITION AND HISTORY

Hepatic encephalopathy or coma refers to that series of neuropsychiatric disturbances and alterations in consciousness found in patients with severe liver disease. Although the association of jaundice with mental deterioration has been recognized for centuries, the first systematic documentation of hepatic encephalopathy was reported by Frerichs in 1860. /1/ The reader is referred to two recent reviews which present an indepth analysis of various aspects of hepatic coma. /2,3/

CLINICAL MANIFESTATIONS

The table shows the four stages in the onset and development of hepatic coma. The earliest features are nonspecific and include frequent euphoria and untidiness. /4/ The sleep

TABLE
STAGES IN ONSET AND DEVELOPMENT OF HEPATIC COMA*

Stage	Mental State	Tremor	EEG† Changes
Prodrome‡	Euphoria, occasionally depression Confusion, absent or difficult to detect Slight slowing of mentation Untidiness	Often present, but slight	Usually absent
Impending coma	*Confusion* Usually euphoria Drowsiness Inappropriate behavior	Usually present and easily elicitable	Almost always present
Stupor	Sleeps most of time, but arousable Confusion, marked	Usually present if patient can cooperate	Almost always present
Semicoma or coma	Unconsciousness May respond to noxious stimuli, or, when deep, may not respond	Usually absent (no muscle tone)	Often present

*Table from Davidson and Gabuzda /5/ with permission of the authors and the publisher.
†EEG is electroencephalographic.
‡Prodrome is recognized often only in retrospect.

rhythm may be disturbed: the patient may be awake and confused at night but may be drowsy or may sleep during the day. A sensitive indicator of early encephalopathy is the presence of constructional apraxia. The match test which requires the patient to construct a five-pointed star from ten matches may be used to test this function.

The second stage of impending coma has more obvious features. The patient frequently manifests confusion, drowsiness, and inappropriate behavior. In addition, he or she may have the well-known flapping tremor (asterixis) and electroencephalographic changes of encephalopathy. It must be emphasized that all these changes are nonspecific. It is the association of these changes with clinically overt hepatic disease that determines whether or not the diagnosis is tenable. /5/

From the stage of impending coma, the patient progresses through increasing lethargy to stupor and finally to total unresponsiveness. Reflexes vary from being absent to being hyperactive. The patients frequently exhibit muscular rigidity. Asterixis usually disappears but the electroencephalogram (EEG) remains abnormal.

The hepatic encephalopathy syndrome may occur as a consequence of acute liver disease, for example, from viral hepatitis. In this setting it is marked by the rapid onset of delirium, convulsions, stupor, and progression to deep coma, often with a fatal outcome. Or it may occur as a result of chronic hepatic disease triggered, for example, by gastrointestinal (GI) bleeding. In this setting, the manifestations may be subtle, frequently reversible, and a clue to the development of the precipitating cause.

Flapping Tremor or Asterixis. The flapping tremor was first identified by Adams and Foley in 1953. /6/ They noted that when a patient's hands and arms were outstretched there appeared at irregular intervals lateral deviation of the fingers, flexion and extension of the fingers at the metacarpal phalangeal joints, and flexion and extension of the wrist. The movements were asymmetrical and tended to occur in bursts. This sign which may also be elicited in all skeletal muscles is believed to be caused by disruption of proprioception at various levels in the nervous system.

This sign may also be seen in uremia, hypokalemia, CO_2 narcosis, and sedative overdose, as well as in hepatic encephalopathy.

Fetor Hepaticus. A specific sign of hepatic encephalopathy is fetor hepaticus. /7/ It is a sweetish, musty odor of the breath caused by the presence of methylmercaptan. /8/ This sign may be difficult to recognize.

Electroencephalogram. The EEG, a sensitive test of hepatic encephalopathy, shows slow one to three per minute delta waves superimposed on normal alpha waves. /9/ These changes are not specific signs of hepatic coma because they may also be seen in other metabolic encephalopathies.

LABORATORY FINDINGS

Hepatic function studies are abnormal, but usually correlate more closely with the extent of the hepatic disease than with the encephalopathy.

Determining ammonia levels in the blood is perhaps the most widely performed test for hepatic encephalopathy. The correlation between ammonia levels and encephalopathy, however, is by no means exact and blood ammonia levels may be normal in severe hepatic encephalopathy. /9/ Arterial rather than venous ammonia levels are a more specific indication of hepatic encephalopathy, although 10% of patients in hepatic coma have normal arterial ammonia levels. /10/

Elevated spinal fluid glutamine is a frequent finding in hepatic encephalopathy. The levels of elevation do not correlate with the severity of the coma, but the level is not elevated in patients with coma from other causes. /11/

Less obvious but frequent accompaniments of hepatic encephalopathy are respiratory alkalosis and hypokalemia with consequent metabolic alkalosis. Alkalosis favors the

formation of the more freely diffusable neutral form of ammonia. This environment will lead to increased transit of ammonia across cellular membranes and the blood-brain barrier. Consequently, alkalosis can profoundly increase the ammonia concentration in the brain.

Hypoglycemia, if present, signals severe hepatic disease with loss of glycogen stores and inability to maintain glucose homeostasis.

PATHOLOGY

No specific hepatic histologic changes are associated with hepatic encephalopathy. The pathology seen is related only to the primary disease process.

Patients with hepatic encephalopathy frequently have cerebral edema. /12/ The histopathologic changes found in chronic hepatic encephalopathy consist of hypertrophy of the protoplasmic astrocytes. These astrocytes participate in the transport of electrolytes and nutrients to the neurons in the brain. It is unclear, however, how this relates to the neurologic disorder.

PATHOGENESIS

A basic assumption of encephalopathy research is that those factors which produce neurologic changes in acute hepatic disease are the same as those seen in chronic hepatic disease. For the purpose of this discussion, I will maintain the same assumption.

Many theories for the pathogenesis of hepatic coma have been advanced. To be viable, a theory must explain the cerebral sensitivity to sedatives and other toxins, the exacerbation of hepatic encephalopathy by protein loading, and the clinical effectiveness of gut sterilization.

The patient with hepatic disease demonstrates increased sensitivity to various endogenous and exogenous toxins. The

cause for this sensitivity may be (a) the presence of a toxin which the liver is unable to remove, for example, ammonia; (b) the absence of some vital substrate which the liver ordinarily provides; (c) the production of a noxious substance by the diseased liver; or (d) some combination of the above theories. What is clear, however, is that at the current time, no one knows the cause of this increased sensitivity. What are the proposed toxins, noxious substances, vital substrates, and other molecular hypothetical bases for encephalopathy?

The true cause of hepatic coma remains unknown. No single etiologic agent has yet been isolated, and the cause may even be multifactorial In addition, the cause may vary from individual to individual. Nevertheless, there are four substances which have been implicated as potential causes of hepatic encephalopathy.

Ammonia

Toxic levels of ammonia remain a leading potential cause of hepatic encephalopathy. /13/ This substance is found in the GI tract, mainly in the large intestine, and is one result of the breakdown of urea and protein by gut bacteria. This ammonia is normally absorbed and transported to the healthy liver by the portal vein where it undergoes conversion to urea via the urea cycle. In liver disease, the portal blood is shunted to the systemic circulation. Hence, ammonia has access to the brain through these porto-systemic shunts.

Much evidence supports the ammonia theory of hepatic encephalopathy. First, elevated ammonia and glutamine (the end product of cerebral ammonia detoxification) are elevated in most patients with encephalopathy. /14/ Second, maneuvers which decrease ammonia production in the gut, or decrease absorption from the gut, are therapeutic in hepatic encephalopathy. Third, administration of ammonia or substances giving rise to it in susceptible individuals leads to stupor. /9/ Finally, individuals who are genetically unable to detoxify ammonia are troubled by stupors and coma. /15/ Ammonia may interfere with cerebral energy metabolism by depletion of Krebs cycle intermediates. For instance, the formation of glutamine consumes one mole of alpha-ketoglutarate for each mole of ammonia that is detoxified.

Short Chain Fatty Acids

Short chain fatty acids such as butyric, valeric, and octanoic acids are increased in the blood of patients with hepatic coma. /16/ However, in the amounts found clinically, no experimental coma could be produced. It may be that these substances act synergistically with other agents to produce their effects.

False Neurotransmitters

Another chemical group which has been implicated in the production of the syndrome is false neurotransmitters. /17/ This theory states that alterations in hepatic function lead to the presence of biogenic amines in the systemic circulation. These amines compete for the postsynaptic binding sites of neurons leading to the failure of transmission of signals by the nervous system. The precursors of these amines which result from the breakdown of protein in the gut, are shunted to the brain and are converted by the nervous system's enzymatic pathways to false neurotransmitters such as octopamine. The presence of these substances could theoretically explain the central and peripheral nervous system phenomena. Clinical evidence presented by Fisher and Baldessarini /17/ and Sherlock et al /18/ support the direct correlation between serum and urinary octopamine levels and degree of hepatic encephalopathy. In addition, administration of L-dopa which theoretically could compete with these substances for the synaptic sites can transiently lessen hepatic coma. /19/ Proof, however, will require demonstration of the presence of the false neurotransmitters at the synaptic sites.

Amino Acids

Finally, various amino acids have been proposed as a cause of hepatic encephalopathy. Iber et al /20/ describe a characteristic amino acid profile in the serum of patients with hepatic encephalopathy. The amino acids usually increased are phenylalanine, tyrosine, and tryptophan. The ratio of these neutral amino acids to the branched chain amino acids may regulate the production of true and false neurotransmitters. /21/ It remains, however, to be shown experimentally how these amino acids exert their effects, if, indeed, they are toxic.

PRECIPITATING FACTORS

In patients with acute hepatic encephalopathy, there are generally no specific precipitating factors other than the primary cause which is usually viral hepatitis. The patients with chronic hepatic encephalopathy, in contrast, are usually in borderline compensation. These individuals usually have a second condition which upsets their state of compensation.

TREATMENT

Treatment is aimed at correcting precipitating factors, reducing blood ammonia levels, and providing general supportive therapy(Appendix B). Measures beyond these goals are experimental and will be mentioned only briefly.

Patients frequently have an electrolyte imbalance related to use of diuretics and to secondary hyperaldosteronism. Hypokalemic alkalosis leads to increased flux of ammonia into the intracellular fluid. Treatment requires replacement of potassium chloride. Hyponatremia occurs in this setting despite an excess of total body sodium indicated by ascites and edema. Fluid restriction corrects this electrolyte abnormality.

Gastrointestinal hemorrhage should be treated appropriately but may be difficult because of coagulation abnormalities.

Because most sedative and hypnotic agents are metabolized by the liver, these agents can lead to serious overdosage in patients with hepatic disease. Overdosages were cited as the second most common cause of hepatic coma in one study. /22/ The administration of these agents, unless absolutely necessary, is inadvisable.

The patient's arterial blood should be checked for oxygen level and oxygen therapy administered for hypoxia. Careful evaluation for possible infection should be made and, when found, antibiotic therapy should be instituted. In patients with ascites, the possibility of spontaneous peritonitis should be considered. /23/ Protein intake

should be restricted. The nursing staff can protect the patient from pressure ulceration, encourage the patient to maintain adequate caloric intake, and observe carefully for signs of treatable complications. Vitamins, especially B groups, should be administered and salt-poor albumin may be administered to expand the ultravascular volume and maintain urine output.

Specific measures to reduce absorption of gut ammonia should be employed. Neomycin can be used to sterilize the gut and to decrease urease-producing intestinal flora. /24/ Neomycin is an aminoglycoside which is about 1% absorbed; however, because of its nephro- and oxotoxic potential, it is not recommended for patients with renal impairment. Therapy is begun with 6 to 8 gm/day and subsequently reduced to 2 gm/day.

A new drug of proven efficacy in reducing ammonia absorption is lactulose. /25/ This is a synthetic disaccharidase which is metabolized in the colon to acetic and lactic acids. The mechanism of its action probably lies in the combined effects of osmotic laxative which acts to clear the gut of urea, and colonic acidification which reduces ammonia absorption. The dosage ranges from 60 to 150 gm/day in three divided doses.

Colonic bypass does ameliorate the symptoms of hepatic encephalopathy, but its benefits are outweighed by high operative morbidity and mortality. /27/

Corticosteroids are not effective for patients with hepatic encephalopathy. In fact, a recent study in acute liver failure has indicated a possible deleterious effect. /28/ They are possibly of benefit in selected patients with chronic active hepatitis and hepatic encephalopathy.

Trials of administration of various essential amino acids are underway. The plan is to change the ratio of neutral to branched chain amino acids, in order to effect a change of neurotransmitter production in the brain.

The proliferation of therapeutic approaches for hepatic encephalopathy has occurred because of the lack of well-defined pathophysiology. Until further specific events producing hepatic encephalopathy can be identified, therapeutic advances must rely on empirical observations.

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The quality of survival is as much the physicians's responsibility as the facts of survival.

COAGULATION ABNORMALITIES IN LIVER DISEASE

Major Richard W. Houston, MC

Coagulation abnormalities are frequently found in patients with liver disease. Because the liver has a central role in human metabolism, the liver affects the clotting mechanism at all levels. It is not surprising, therefore, that these clotting defects are often quite complex. Abnormalities which have been implicated as causes of blood clotting disorders in liver disease include: clotting factor deficiencies; structurally abnormal clotting factors; circulating anticoagulants; abnormal fibrinolysis; platelet abnormalities; disseminated intravascular coagulation (DIC); and various combinations of the above. This paper will discuss the role of the liver in normal hemostasis and review clotting abnormalities encountered in patients with liver disease.

THE LIVER IN NORMAL HEMOSTASIS

A schematic representation of the clotting and fibrinolytic mechanism is shown in the figure. Factors I, II, V, VII, IX, X, and probably VIII, are synthesized in the liver. /1,2/ It is possible that factors XI, XII, and XIII may also be of hepatic origin, however, there is no conclusive evidence to support this theory at the present time. /1/

Vitamin K Dependent Factors

Naturally occurring vitamin K is lipid-soluble and cannot be synthesized by mammals; it is furnished through dietary intake and by intestinal flora. Vitamin K is essential for production of clotting factors II, VII, IX, and X. Although the subject of extensive investigation, the exact function of vitamin K in the synthesis of these factors is still unknown. Current evidence suggests that vitamin K acts only after formation of protein precursors to the clotting factors. /3,4/ These polypeptide precursors lack

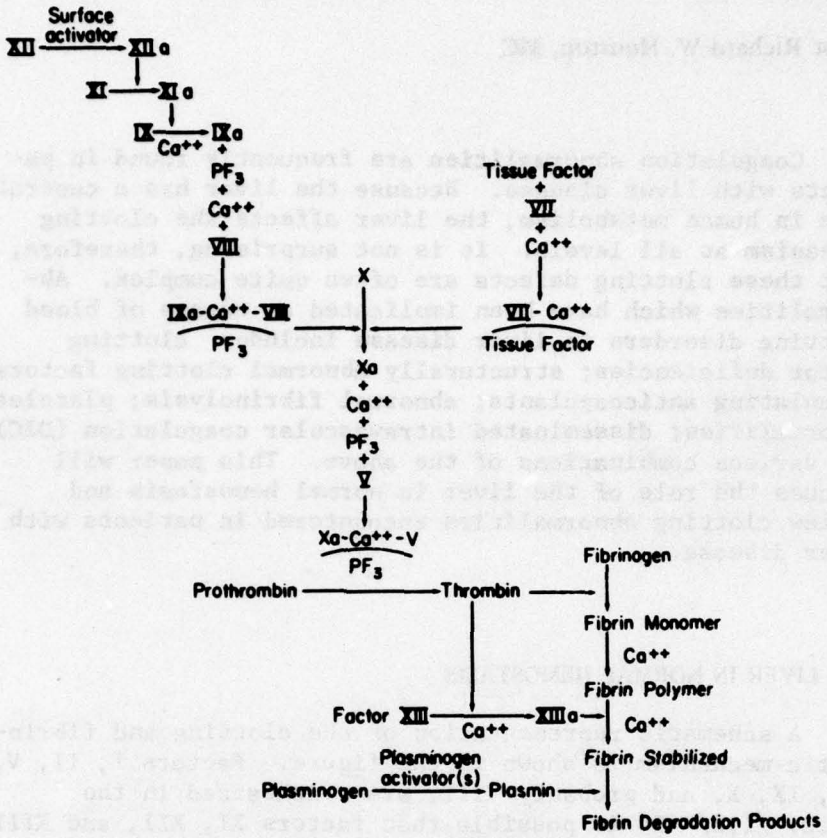

Figure. A schematic representation of the clotting and fibrinolytic mechanism. PF_3 refers to platelet factor III, while *a*, following the Roman numeral nomenclature, refers to the "activated" form of that factor.

clot promoting properties. /5,6/ In hepatic parenchymal disease synthesis of the precursors is deficient. /7/ Vitamin K deficiency prevents the formation of functional clotting factors, but it does not prevent formation of their polypeptide precursors. /8,9/ These data strongly suggest that precursors to factors II, VII, IX, and X are produced in the hepatocyte and that vitamin K is necessary for the formation of these factors from the precursors. The specific structural change induced by vitamin K, which converts the precursor polypeptide to a clotting factor, remains unclear.

However, the following conclusions seem justified by current data: /1/

- Vitamin K itself is not a part of the clotting factor molecule.
- Vitamin K does not maintain the circulating level of these factors by preventing their degradation.
- Vitamin K does not appear to affect the release of the completed clotting factor from hepatocytes.
- Vitamin K does not appear to affect the transcription step of DNA to M-RNA.

The vitamin K dependent clotting factors have a number of characteristics which suggest that their basic chemical structure is similar. /10/ Because of their extraordinary similarities, which are unshared by other clotting factors, this group has been labeled the "prothrombin complex."/11/ An explanation for the existence and significance of the unusual similarities noted in vitamin K dependent clotting factors is lacking at the present time.

Fibrinogen and Factors V and VIII

In addition to the vitamin K dependent factors, the liver also produces fibrinogen, factor V, and probably factor VIII. There is considerable evidence that fibrinogen is synthesized in the liver by the parenchymal cells /12,13/, but high levels of fibrinogen have been found after hepatectomy, suggesting that there are also extrahepatic sites of synthesis. Factor V is synthesized largely, or perhaps exclusively, by the liver and its level is unaffected by vitamin K deficiency in coumarin derivatives. /13/ There is now good evidence that the liver is a source of factor VIII synthesis, although much is produced in extrahepatic sites. /14/ The spleen has also been shown to play a role in storage and release of factor VIII.

In addition to the production of clotting factors, there is evidence that the normal liver possesses clearance mechanisms which remove active clotting factors from the circulation, thus preventing intravascular coagulation. /1/

Although it is assumed that these hepatic clearance mechanisms are physiologically important, their true significance in coagulation homeostasis remains to be demonstrated.

Fibrinolytic System

The relationship between the liver and the fibrinolytic system is a matter of controversy. The ability to digest fibrin resides in one or more plasma proteases known as plasmin. This protease has a broad spectrum of activity. Besides digesting fibrin, plasmin hydrolyzes fibrinogen, inactivates factors V, VIII, IX, and prothrombin. It also digests ACTH, glucagon, and somatotropin and converts the first component of complement to C_1 esterase. /10/ In normal blood, plasmin is in the form of an inactive precursor, plasminogen. Plasminogen is found largely in eosinophils but is thought by some to be synthesized also in the liver. /15,16/ Plasma possesses plasmin inhibitory activity. Antiplasmin, a protease inhibitor, is synthesized by the liver and evidence suggests that it is identical to alpha-1-antitrypsin. /1/ Antithrombin III, alpha-2-macroglobulin, and C_1 esterase inhibitor are additional plasma proteins which have antiplasmin activity. Plasminogen activator activity can normally be detected *in vivo*. If plasmin were allowed to become excessively active in the body, clots might dissolve before wound healing was complete. Evidence is available that the normal liver rapidly clears plasminogen activator from the circulation, thus regulating the activity of the fibrinolytic system.

ABNORMAL HEMOSTASIS IN LIVER DISEASE

Vitamin K Deficiency

Vitamin K deficiency results in decreased levels of clotting factors II, VII, IX, and X (the prothrombin complex) while other factors synthesized by the liver remain normal or even increase in concentration. Factor VII which has the shortest half-life is reduced first, followed in sequence by factors II, X, and IX. /17/ Clinical conditions which may result in insufficient levels of vitamin K include malnutrition with altered bowel flora, biliary obstruction,

malabsorption, intoxication with coumarin anticoagulants, and the neonatal state.

Dietary deficiency of vitamin K is extremely rare in normal adults, and vitamin K producing bacteria within the gut must be altered before vitamin K deficiency becomes evident. /18/ Sterilization of the intestinal tract with broad spectrum antibiotics does not usually depress vitamin K dependent clotting factors in healthy people, but this may occur in clinically ill patients with little oral intake.

Vitamin K deficiency has long been recognized as a complication of diseases associated with biliary obstruction and malabsorption syndromes. In obstructive jaundice, vitamin K is absorbed poorly because bile salts are unable to enter the duodenum. Similarly, lipid malabsorption and the administration of cholestyramine reduce reabsorption of bile salts from the gut. Because vitamin K is lipid-soluble, its optimal absorption from the gastrointestinal tract requires the presence of bile salts and probably pancreatic lipase as well. /10/ While the susceptibility to hemorrhage in obstructive jaundice is well recognized, the finding of clinically significant hemorrhage in malabsorption syndromes is uncommon. /19/

The majority of neonates have low levels of the prothrombin complex, particularly after the first three days of life. The cause is unknown, but is believed to be related to lack of bacterial flora, lack of vitamin K intake, or poor utilization of vitamin K by the immature neonatal liver. Normally, adult levels of the vitamin K dependent clotting factors are reached during the first year of life. /20/

Coumarin anticoagulants produce a relative deficiency of vitamin K probably through interference with a vitamin K binding protein at the hepatocellular level. /21/ The action of coumarin drugs is potentiated in patients with preexisting liver disease. It has also become well-established that various medications, usually through pharmacological effects on the liver, act to inhibit or enhance the effect of oral anticoagulants. /22/ Those drugs which decrease the coumarin effect act through induction of microsomal enzymes. This decrease results in increased

metabolism and a shortened half-life of the anticoagulant. /23/ Several mechanisms by which drugs potentiate coumarin compounds include:

- Inhibition of hepatic degradation of the anticoagulant.
- Increase in the affinity of hepatic receptors for warfarin.
- Direct interference in the synthesis of vitamin K dependent factors.
- Inhibition of vitamin K absorption from the gut.
- Displacement of coumarin from binding sites on plasma proteins.

Hepatocellular Disease

The coagulation abnormalities resulting from hepatocellular damage are much more complex than those related to vitamin K insufficiency alone. As was indicated earlier in this paper, the liver is involved at every level of the coagulation process; thus, it is reasonable to assume that parenchymal liver disease is capable of interferring with the clotting mechanism in a number of different ways. Frequently, it is difficult to determine whether one or several of the possible abnormalities is contributing to the bleeding disorder in a given patient. In most cases, however, the coagulation defect will fall into one or more of the following categories:

- Decreased synthesis of clotting factors.
- Increased utilization of clotting factors.
- Production of abnormal clotting factors.
- Platelet dysfunction.

Decreased Synthesis of Clotting Factors. The clotting factors most likely to be reduced in parenchymal liver disease are factors II, VII, IX, and X. Their level is a sensitive indicator of hepatic function and is often reduced before other liver function tests become abnormal. Fibrinogen and factor V may also be reduced in severe hepatocellular disease. Their decrease can result from either impaired synthesis or increased utilization through DIC or excessive fibrinolysis. Hyperfibrinogenemia and increased levels of factor V are characteristic of cholangitis, extrahepatic biliary obstruction, and liver cancer. /17/

Although factor VIII is probably produced in the liver, extrahepatic synthesis is sufficient to maintain normal or increased levels even in severe parenchymal disease. /2/

Factor XIII is necessary for the production of a normal blood clot and is decreased in hepatocellular disease. The deficiency appears to correlate with the severity of parenchymal damage; however, no direct relationship exists between low levels of factor XIII and clinically significant hemorrhage in patients with liver disease. /25/

A deficiency of surface factors XI and XII contributes to the defect in thromboplastin generation in severe liver disease but is not believed to be a sensitive parameter of liver function. /17/

In addition to deficient levels of various clotting factors, the production of structurally abnormal fibrinogen has been noted in patients with severe hepatocellular damage. /26/ Acquired abnormal fibrinogen has also been described in a patient with hepatoma. /27/ Although acquired abnormalities of other clotting factors have not been detected, their existence is possible. Hereditary disorders characterized by structurally abnormal and biologically inactive clotting factors are well-known. Abnormal forms of factors I, II, VII, VIII, IX, and X have been reported. /1/

Increased Utilization of Clotting Factors. Increased utilization of clotting factors occurs as a result of DIC, excessive fibrinolysis, and possibly proteolysis. There is strong evidence to support the concept that DIC occurs

in hepatic insufficiency, based on both animal and human studies. /2/ Disseminated intravascular coagulation has been described in acute hepatic necrosis /28/ and in cirrhosis /29,30/. Theoretically, systemic coagulation is activated by thromboplastic substances from damaged hepatic cells which the impaired hepatic clearance mechanism has been unable to remove from the circulation. Both fibrinogen and platelet thrombi are formed following thrombin generation. Hemorrhage then ensues as large amounts of clotting factors are consumed. Secondary fibrinolysis occurs and adds to the coagulopathy by proteolysis of some of the same clotting factors acted upon by thrombin and by formation of fibrin degradation products. Fibrin degradation products are usually ascribed to degradation of fibrin by plasmin, but may represent circulating, incompletely polymerized fibrin, or complexes of fibrin monomers and fibrinogen or fibrin-degradation products. /11/ Thus, in DIC the following clotting abnormalities are seen clinically:

- Decreased levels of factors I, II, V, VIII, XIII, platelets, plasminogen, antithrombin, and antiplasmin.
- Increased fibrinolysis.
- Increased fibrin degradation products.

Unfortunately, the diagnosis of DIC can be difficult to establish, and it becomes even more difficult in the presence of hepatic insufficiency. Because of the multiple factors contributing to coagulation defects in liver disease, many of the abnormalities characteristic of DIC can be attributed to other causes. For example, low levels of fibrinogen, prothrombin, factors V, XIII, and plasminogen could be related to impaired hepatic synthesis rather than to consumption. Thrombocytopenia in liver disease can result from splenic sequestration and decreased production as well as increased utilization; reduced levels of fibrinogen could represent primary fibrinolysis rather than DIC.

Primary fibrinolysis has been reported to occur in cirrhosis with an incidence varying from 20% to approximately 90%. /31,32/ However, there is little evidence of

excessive fibrinolysis in patients with acute liver disease. Although the presence of primary fibrinolysis in chronic liver disease is well-documented, it may be difficult to differentiate from fibrin degradation secondary to DIC, as noted above. The mechanism of increased fibrinolytic activity in liver disease is not completely understood. Current evidence suggests it is related to an excess of available plasminogen activator resulting from decreased levels of antiplasmin and delayed hepatic clearance of plasminogen activator. /2/

Circulating Anticoagulants. The role of circulating anticoagulants in liver disease is a controversial topic. The literature contains many conflicting reports regarding their activity in various types of liver disease. The present consensus is that antithrombins probably behave irregularly in chronic hepatitis, biliary cirrhosis, and cholestasis, but are increased in obstructive jaundice and reduced in cirrhosis. /3/ Antithromboplastin activity has been described as diminished in both acute and chronic hepatocellular disease. /2/ Their true importance in clinical bleeding states remains unclear.

Platelet Abnormalities

The association of thrombocytopenia with chronic liver disease and portal hypertension is a common clinical finding and has been well-documented in the literature. The pathogenesis has also been extensively studied and multiple etiologies identified. Splenic sequestration /33/, decreased production, and reduced platelet survival /34/ have all been reported in patients with liver disease and thrombocytopenia. Qualitative platelet abnormalities have also been reported. Mandel and Lazerson /35/ noted platelets low in thromboplastic activity and Thomas et al /36/ have found impaired platelet aggregation. In some patients with cirrhosis, reduced platelet levels may be related to a deficiency of folic acid. /11/ It is unknown if this deficiency is caused by inadequate dietary intake or a defect in metabolism. Because the most common cause of chronic liver disease in the United States is alcohol abuse, the toxic effect of alcohol on platelets should be considered. The thrombocytopenia can be quite severe and is not necessarily associated with folic acid or vitamin B_{12} deficiency. /37,38/ Decreased platelet survival appears to be the underlying mechanism.

Thrombocytopenia has also been reported in acute infectious hepatitis but is uncommon and the pathogenesis is unclear.

COAGULATION TESTS IN LIVER DISEASE

The coagulation tests most commonly used in routine screening of patients with liver disease include the prothrombin time, partial thromboplastin time, and platelet count. The prothrombin time assesses the extrinsic pathway and may indicate abnormalities of the factors I, II, V, VII, and X. It is frequently abnormal in obstructive jaundice or hepatocellular disease. The partial thromboplastin time is a test of the intrinsic system. It is influenced by all factors except VII and platelets. It can also be abnormal in obstructive jaundice or hepatocellular disease but is rather insensitive to mild factor deficiencies. Although these clotting studies are useful as screening tests, it must be remembered that clinically significant decreases in clotting factors may be missed by both the prothrombin time and the partial thromboplastin time. In addition, platelets may be in an acceptable range quantitatively, but be abnormal qualitatively. Therefore, if a patient's history or clinical presentation suggests a severe hemorrhagic disorder more specific tests are required. For example, euglobulin lysis time, fibrin degradation products, and fibrinogen levels would be helpful in patients with fibrinolysis or DIC. Specific assays of individual clotting factors may also be required. In general, the coagulation abnormalities characteristic of DIC, primary fibrinolysis, and severe liver disease can be separated by the following parameters.

- Platelets are reduced and the euglobulin lysis time is normal in DIC, while in primary fibrinolysis, platelet levels tend to be normal and the euglobulin lysis time is shortened.

- Hepatocellular disease tends to have normal to elevated levels of factor VIII with decreased levels of factors VII and IX, while in DIC factor VIII is low and factors VII and IX are normal. However, in spite of the sophisticated coagulation studies available, it may still prove impossible to determine which factor or combination of factors is responsible for bleeding in a given patient with liver disease.

TREATMENT

Although up to 85% of patients with liver disease demonstrate at least one abnormal clotting test, only about 15% develop clinically significant bleeding. /2/ Unless the clotting abnormality is severe, it is usually a contributing factor rather than a cause of hemorrhage. Local causes such as esophageal varices, gastritis, or ulcers should be looked for and treated in addition to managing the coagulation defect.

Vitamin K Therapy

Vitamin K therapy, with doses in the range of 10 mg per day, rapidly corrects the coagulation defect related to vitamin K deficiency as in obstructive jaundice.

However, in most cases where prolonged prothrombin time and bleeding are associated with heptic parenchymal disease, vitamin K will be of no benefit. Occasionally, in patients with severe jaundice and hepatocellular disease, high doses of vitamin K, up to 50 mg per day, will shorten the prothrombin time. This fact suggests that a component of intrahepatic biliary obstruction is also present in these cases. Thus, vitamin K can be of diagnostic as well as therapeutic value in some patients with liver disease.

Replacement Therapy

When coagulation studies indicate that the defect is related to decreased synthesis of clotting factors, replacement therapy with fresh frozen plasma or fresh whole

blood should be tried. Although factors II, VII, IX, and X are stable during storage, fresh plasma or blood is the only good source of actor V. /1/ Unfortunately, these transfused factors disappear rapidly from the circulation and up to 200 ccs every four hours may be required to maintain normal levels. /10/ In clinical situations where this volume load is unacceptable, concentrates of the vitamin K dependent factors can be used to sustain adequate levels and avoid overloading the circulation. Hypofibrinogenemia secondary to decreased synthesis can be effectively treated with intravenous infusion of concentrated human fibrinogen. It is important to remember that these concentrates are capable of transmitting hepatitis. Platelet transfusions may also be required when thrombocytopenia is a significant factor in bleeding.

If excessive fibrinolysis is present in association with major hemorrhage, an antifibrinolytic agent such as Epsilon aminocaproic acid (Amicar®) may be of benefit. Amicar® is a potent inhibitor of plasminogen activation and is available for intravenous or oral use. It carries a risk of arterial or venous thrombosis and other side effects include hypotension, dizziness, diarrhea, and abdominal pain. It is contraindicated in the presence of DIC and should be avoided in the presence of thrombocytopenia or normal factor VIII levels unless given with heparin. Although there are data to suggest that the use of heparin is beneficial in DIC associated with liver disease /39/, its use is rarely indicated and should be considered only when the diagnosis of DIC is well established. It is imperative that appropriate laboratory facilities be available for following and evaluating patients in whom an antifibrinolytic agent or heparin therapy is used for management of hemorrhage.

A treatment summary for coagulation abnormalities in liver disease is listed in Appendix C.

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Nature always sides with the hidden flaw in the system.

Democratic Principles:

A. Biologic phenomena cannot be determined in a democratic manner.

B. The decision for or against a given mode of therapy cannot be made by plebiscite.

Sutton's Law:

William Dock, M.D., on ward rounds when he discovered that every test had been done except the appropriate one, suggested that the student follow Sutton's Law, which he defined as follows: Willy Sutton, the bank robber, was asked why he always robbed banks rather than hotel clerks, filling stations, or other easy marks. He replied, "Because that's where the money is."

Jolley's Dictum: The heart serves to pump blood to the liver.

FULMINANT HEPATIC FAILURE

Major John J. Jolley, MC

Massive necrosis of liver cells for whatever reason may cause a sudden and severe impairment of hepatic function, leading to a clinical syndrome manifested by progressive jaundice, shrinkage of the liver, severe clotting abnormalities, and encephalopathy with coma. This syndrome of rapid deterioration in severe, acute liver disease is called fulminant hepatic failure (FHF). /1/

FREQUENCY AND ETIOLOGY

Viral hepatitis accounts for more than half of the cases of FHF in the United States. Fulminant hepatic failure occurs in approximately 0.2% to 1.0% of patients with acute viral hepatitis, with the incidence of hepatitis virus A approaching that of hepatitis virus B. Halothane-associated hepatitis accounts for approximately 25% of FHF; other drug sensitivities, direct toxins, and miscellaneous disorders such as fatty liver of pregnancy and Reye's syndrome account for the other 25%. /2/ The English authors report acetaminophen overdose, resulting in a toxic hepatitis, as an important cause of FHF in the United Kingdom. /3/

CLINICAL SETTING

Fulminant hepatic failure has a clinical parallel in the syndrome of the "hepatectomized animal", which consists of hypoglycemia followed by decerebrate and decorticate rigidity. The animal dies within 10 days after lapsing into coma, with unrelenting hypotension and respiratory failure. /2/ In humans, a patient with viral hepatitis usually has general systemic symptoms of nausea, anorexia, and malaise for one to two weeks. He then undergoes sudden and dramatic clinical deterioration with progressive hepatic coma, vasomotor collapse, and respiratory failure. This fulminant deterioration

usually occurs over two to four days but may be telescoped into several hours. /4/ A second, less frequent, presentation of FHF is progressive hepatic coma without antecedent systemic illness. Elderly patients often present with a progressive deterioration over one to two months, called "subacute fatal hepatitis." /1/

CLINICAL EVALUATION

Laboratory tests are helpful in determining which patients with acute liver disease have sufficient liver cell impairment to develop progressive hepatic coma. The onset of FHF is heralded by a marked elevation in serum glutamic oxalocetic transaminase (SGOT) activity with a rapid return toward normal, so that the SGOT is normal at time of death. /5/ The elevation of the SGOT during an episode of hepatitis is not prognostic. Three laboratory studies are helpful in singling out those patients who are at risk of developing FHF in acute liver injury /6/: (1) prothrombin time (prolonged longer than four seconds; (2) white blood cell count (WBC) (greater than 12,500 cu/mm); and total bilirubin concentration (greater than 20 mg/dl).

Of these tests, prothrombin time is the most sensitive indicator of functional hepatic cell mass. One-third of those patients with a prothrombin time of less than 20% who develop Stage II coma regress, and two-thirds progress to deeper coma. /1/ In patients with progressive disease, survival depends upon their age and the depth of their coma; 20% to 25% of patients under age 40 who develop Stage IV coma survive, while the survival rate over age 40 is 6% or less. /7/

Bedside evaluation of the acute liver disease patient often results in detection of early signs of FHF. The clinician should monitor the patient's liver for rapid decrease in size, abdominal girth for ascites, sleeping habits (sleep disturbances occur early in coma), odor (fetor hepaticus develops early) and constructional apraxia. (Checking the patient's ability to form a star pattern with toothpicks often works well.)

TREATMENT

Mortality with Stage IV coma is 80% to 90%. /8/ There is no substantial evidence that FHF responds to any specific treatment; rather, treatment is supportive in the hope that liver regeneration will occur. Regeneration begins in the second week as measured by serum alpha-fetoprotein; however, this is not necessarily a good prognostic sign. /9/ The fact that death most often occurs during active hepatic regeneration strongly reflects the need for continuous supportive therapy. Correlation between necrosis found on biopsy and prognosis is poor, although, when studied with stereohistopathology, an assessment of functional hepatic volume can be made. /10/ Patients who undergo FHF in the course of acute liver disease generally have normal liver biopsies after recovery /11/, again emphasizing the need for supportive care through the acute stage of the illness. Therapeutic guidelines for FHF are given in Appendix C.

Treatment can be subdivided into two categories: supportive treatment and experimental, specific treatment.

SUPPORTIVE TREATMENT

Accepted (supportive) therapy is based on four general clinical symptoms:

1. *Decreased brainstem function:* coma, respiratory arrest, vasomotor collapse, and cerebral edema.

2. *Metabolic disorders:* hypoglycemia, electrolyte disorders, acid-base disturbances, and renal failure.

3. *Bleeding disorders:* failure of hemostasis and gastrointestinal bleeding.

4. *Increased susceptibility to infection.*

Decreased Brainstem Function

Although the pathogenesis of hepatic coma in FHF is not as clearcut as in recurrent encephalopathy with protein intolerance of chronic liver disease, the same principles, as outlined elsewhere in this Symposium, are followed. Cerebral edema occurs in 50% of patients with FHF /12/, generally in a younger population (under 30). The etiology is not clear; both focal (vasogenic) and diffuse (cytotoxic) edema have been reported. Osmotheraphy may be tried, although at the present time, there is no evidence that it is successful. Although focal findings and abnormalities of the pupillary response to light, ciliospinal, oculovestibular and oculocephalic reflexes may be seen in FHF, they should arouse suspicion of hypoglycemia or focal disease. /8/

Vasomotor collapse is treated with vasopressors following volume replacement and a search for other causes of shock, such as bleeding and infection. Respiratory difficulty is handled with assisted respiration. In Stage III coma, most authorities recommend a tracheostomy as prophylaxis.

Metabolic Disorders

The liver is the source of blood glucose during fasting; therefore, it is not surprising that hypoglycemia often dominates the clinical features of FHF. /13/ Hypoglycemia can produce any of the neurologic findings of hepatic encephalopathy, as well as focal findings. About half of the patients with FHF develop hypoglycemia, so that frequent monitoring of blood sugar is mandatory.

Fifty to 75% of FHF patients develop azotemia. /14/ Generally, the renal dysfunction mimics the functional renal failure seen in the end stage of cirrhosis; 5% to 20% of these patients have volume depletion and a trial of fluids should be administered under central pressure measurement. An additional one-third of azotemic patients are of the acute tubular necrosis variety. Electrolyte and acid-base problems vary; generally, these patients have early hypokalemia and respiratory alkalosis and late renal-tubular acidosis in addition to metabolic acidosis. /15/ Impaired free water clearance, even in the absence of overt renal failure, often leads to hyponatremia.

Bleeding Disorders

Gastrointestinal bleeding occurs in two-thirds of patients with acute liver disease and is often fatal. The bleeding is usually the result of gastric erosion, although diffuse oozing from the esophagus and small bowel, as well as the development of acute gastroesophageal varices, may occur. Frequent antacids and nasogastric suction are not associated with decreased gastrointestinal bleeding, but in a randomized study /16/, Cimetidine was shown to virtually abolish gastrointestinal bleeding.

Hemostasis is almost impossible to unwrap in FHF. The liver is the major source of clotting factors (except for factor VIII) and the ability of blood to clot may decay rapidly with FHF. Vitamin K should be given prophylactically and fresh frozen plasma should be administered as needed; because of its high salt and fluid content, the fresh frozen plasma must be administered with central pressure monitoring. Most patients will develop pulmonary edema with nonjudicious use of fresh frozen plasma. Disseminated intravascular coagulopathy, both generalized and localized to the liver, may be impossible to differentiate from the hemostatic disorders in FHF. /17/ These diagnostic difficulties have led to several clinical trials of heparin therapy, but heparin appears to be of no benefit in FHF.

Increased Susceptibility to Infection

Serious infections occur in 50% of FHF patients and are directly responsible for the death of 25% of them. Most infections are associated with urinary catheters and loss of pulmonary defense in coma and are preventable, although there is a marked inhibition of polymorphonuclear cell metabolism by a factor produced in FHF. /18/ The significance of this factor is unknown, but it appears to be removable by charcoal hemoperfusion. /19/ Prophylactic antibiotics should not be used; continuing investigation and prevention are the only mainstays of therapy.

EXPERIMENTAL SPECIFIC TREATMENT

Immune Therapy

Corticosteroids are associated with an increased mortality rate when used in patients with FHF. Hyperimmune globulin provides no significant prolongation of patient survival in FHF. /20,21/

Metabolic Therapy

Metabolic therapy at present is experimental and heroic, in that the pathophysiology of FHF is unknown. The liver has four major metabolic functions: biosynthesis, storage, removal, and biotransformation. The question in FHF is whether there is an accumulation of toxins secondary to decreased storage and removal, or a lack of release of needed factors secondary to decreased biosynthesis or biotransformation. Thus, removal of toxins may be of no benefit. Several toxins are known to accumulate in FHF but none have consistently been correlated with coma.

All specific nonimmunologic treatment is based on the premise that if the patient's general condition can be maintained and the complications controlled, then survival is possible because of the capacity of the liver to regenerate. It should be noted, however, that little is known concerning regeneration following FHF. After extreme insult, regeneration may be impossible. Present techniques of temporary support are intended either to filter supposed toxins or to replace the circulating blood volume with exchanged fluid. These procedures are generally experimental and have not been shown to alter mortality rates. The decision to use these mechanisms usually is made for a patient in the Stage IV or late Stage III coma, and when the technical ability and equipment for operation are available. The temporary improvement which results can be assessed by the electroencephalogram and by the patient's mental state.

Techniques Which Rely on Filtering

Hemodialysis /22/ was probably the first technique used because it has long been known that ammonia is dialyzable and that ammonia is associated with coma. Scattered case reports which show no overall change in mortality have been reported, but a thorough study has not been done. Hemodialysis has been considered ineffective although, to date, no data are available to substantiate this opinion. Hemodialysis removes small molecular weight, nonprotein-bound substances. In an attempt to remove protein-bound substances with larger molecular weight, hemoperfusion was devised. /20/ In this procedure, blood is percolated through absorbants to remove potentially dialyzable toxins. A recent study shows that 14 of 37 patients treated with hemoperfusion survived Stage III and Stage IV coma. /23/ A more invasive technique of filtering is that of cross circulation with live partners /24/ (humans and primates) and cadavers /25, 26/. These techniques have been of little benefit and fatal immunologic reactions have occurred in both patients and partners.

Replacement Therapies

Perhaps the simplest method of replacement is based on the neurotransmitter hypothesis. This hypothesis states that there is interference with central nervous system transmission by inhibition, loss, or competition (by false neurotransmitters) in FHF. Animal studies show changes in the amount and function of neurotransmitters, but no specific therapy has been developed. Levodopa temporarily reduces the depth of the coma /27/ and results in a more favorable electroencephalogram, but does not alter mortality rates. Exchange procedures are based on the premise that toxins can be removed and needed substances added to improve the metabolic condition. Whole body exchange transfusions have been reported /28, 29/ in which venous blood was drained and whole blood transfused via an arterial line, with 10 to 12 units of blood per exchange. Initial case reports showed improved survival rates, but when subjected to a prospective trial /30/, whole body exchange transfusion did not alter mortality rates. Plasmapheresis is an exchange transfusion wherein blood is removed and red blood cells are reinfused with new plasma. A small, prospective study /31/ study showed this to be of

no benefit for patient survival. It has been suggested that cell-separator techniques may have potential in improving plasmapheresis. /32/ Perhaps the most heroic of these exchanges is hypothermic total body washout. /32/ In this procedure, the patient is cooled and exsanguinated. Just prior to death, the body is washed with hypothermic Ringer's solution and the blood volume is replaced with plasma and packed cells. Workers in this field believe total body washout to be quite useful, but their enthusiasm has not been supported by data or a prospective trial.

Additional experimental techniques such as affinity chromotography, alteration of hepatotropic factors, and liver transplantation are under investigation. The effectiveness of any specific therapy is difficult to assess in a disease with such an unpredictable history.

CONCLUSION

Fulminant hepatic failure continues to be a frustration for the clinician. Knowing that those patients who survive FHF are left with no demonstrable chronic liver disease, and recognizing the potential of the liver to regenerate, the clinician is desperate to develop a mode of therapy to actively support the patient with acute liver disease. Despite past heroic efforts, general medical support remains the basis of our therapy.

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Curing:

A. The leaving of an order never cured a patient.

B. No patient was ever cured by a laboratory determination.

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Merskey's Rules:

A. Do a silly test and you get a silly answer.

B. In the hospital more deaths occur in bed than out of bed, so get the patient out of bed!

C. Any drug can do anything!

●●●●●●●●●●●●

Rumple's Rule:

No hospital staff physician is totally worthless; he can always be used as a horrible example.

●●●●●●●●●●●●

Patient's Rule (concerning his symptoms):

It's not a matter of life or death – it's much more important than that.

The Chief's Basic Rules:

A. The Chief is right.

B. In the impossible hypothesis that a subordinate may be right, rule A becomes immediately operative.

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Loeb's Laws of Medicine:

A. If what you're doing is working, keep doing it.

B. If what you're doing is not working, stop doing it.

C. If you don't know what to do, don't do anything.

D. Above all, never let a surgeon get your patient.

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Butler's Rule: An invasive procedure must have a very specific indication.

Present Concepts, Gastroenterology Symposium, Fall 1977

VARICEAL HEMORRHAGE

Lieutenant Colonel Melvin L. Butler, MC

Variceal hemorrhage accounts for one-fourth to one-third of massive upper gastrointestinal hemorrhage. The hazards of rupture of a varix, the subsequent blood loss, and the urgency for treatment by all modalities can only be understood by examination of the role of the liver in vascular hemostasis (discussed elsewhere in this Symposium), and by knowledge of the pathophysiology of varices and their location.

PATHOPHYSIOLOGY OF VARICES AND THEIR LOCATION

The Anatomy of the Portal Vein and the Microcirculation of the Liver

The portal vein is formed by the union of the superior mesenteric vein and splenic vein and drains blood from the stomach, intestine, spleen, and pancreas. Portal hypertension results from an anatomical abnormality or functional obstruction to blood flow in the portal venous system at any point from its origin to its exit into the systemic circulation via the inferior vena cava. Blood in the portal vein is normally at a pressure of 5 mm of Hg to 10 mm of Hg. Portal hypertension is believed to be present when the intrasplenic pressure exceeds 15 mm of Hg to 17 mm of Hg and when wedged hepatic vein pressures are more than 4 mm of Hg above inferior vena cava pressure. /1/

In the liver the portal vein divides into many small branches and the microcirculation of the liver is such that blood moves from the outside of the lobule to the center. Each portal vein in the portal triad usually gives rise to three branches that open directly to the sinusoids. The sinusoids then anastomose freely at all levels between the portal vein and the central vein. In the normal liver, only one-fifth to one-sixth of the sinusoids are used at ordinary blood flow. As the amount of portal blood flow increases, more sinusoids are used. After the flow has increased

five to six times the normal level, the portal pressure rises abruptly (Figure 1). The principal resistance to

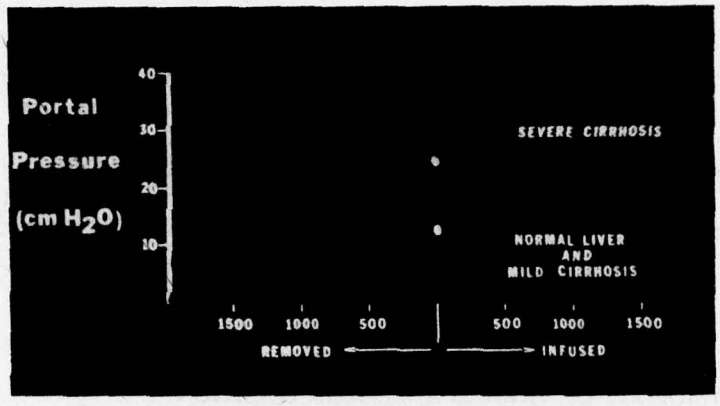

Figure 1. Effect of varying portal flow on portal pressure.

flow occurs at the level of the liver sinusoid and through the tortuous collaterals. The portal pressure always equals flow times intrahepatic resistance.

In decompensated portal hypertension, reverse flow of the portal blood is established through collateral circulation. The esophageal veins dilate because of the inability of their muscular and elastic elements to withstand the elevated intraluminal pressure. With the forced dilatation, the walls become thin, and the veins become tortuous and sacculated.

Causes of Portal Hypertension

The classification of portal hypertension (Table) can be approached in several ways, depending on whether or not the obstruction to flow occurs before the hepatic sinusoid (presinusoidal) or in and beyond the hepatic sinusoid (sinusoidal and postsinusoidal).

TABLE*
CLASSIFICATION OF PORTAL HYPERTENSION

	Pressure			
	Intra-splenic	Wedged hepatic vein	Type	Example
Presinusoidal	Raised	Normal	Extrahepatic	Block portal or splenic vein
				Increased splenic flow
			Intrahepatic	Schistosomiasis
				Congenital fibrosis
				Portal zone infiltrations
Postsinusoidal	Raised	Raised	Intrahepatic	Cirrhosis
				Veno-occlusive disease
			Extrahepatic	Block hepatic vein

*From Sherlock S: *Diseases of the Liver and Biliary System.* Philadelphia, F.A. Davis, Co., 1968. Used with permission of the author and publisher.

Collateral vessels which become functional in portal hypertension are classified into two groups: (a) hepatopetal (flowing toward the liver), and (b) hepatofugal (flowing away from the liver).

The hepatopetal collateral circulation occurs only when the intrahepatic vasculature is normal and obstruction is limited to the portal vein. Hepatofugal flow is by far the more common type of collateral flow. The vessels that form such a circulation include: coronary veins; superior hemorrhoidal, umbilical, and periumbilical veins; and retroperitoneal veins of Retzius.

Veins from the small segment of the abdominal esophagus drain into the left gastric vein, as do the veins from the fundus and cardia of the stomach. The veins from the upper esophagus direct blood into the inferior thyroidal vein and veins from the entire thoracic esophagus send blood into the azygos and hemiazygos veins and finally drain into the superior vena cava. These venous systems are connected by small veins which lie in the esophageal submucosal plexus and which are ordinarily closed. Whenever portal hypertension develops, the pressure in the portal system is transmitted through preexisting collateral channels to dilate the esophageal veins and produce large varices.

Almost by definition, the presence of esophageal varices means that gastric varices have already developed. The most important collateral blood vessels linking the portal and systemic veins are those between the left coronary vein and the azygos vein. This results in submucosal varices of the lower esophagus; however, localized varicose formations may also occur at other sites. These other facets of collateral venous dilatation and flow are found in the mesentery, around the diaphragm and gallbladder, in the retroperitoneal area, jejunum, terminal ileum, and cecum, and are also subject to rupture and hemorrhage.

Factors Which Predispose to Variceal Bleeding

In an individual case, it is not possible to state why a varix bleeds. It is much more puzzling why so few patients with varices do bleed. It is estimated that bleeding occurs in only 30% of cirrhotic patients with known varices. /2/ The elapse of time from the diagnosis of varices to the first major hemorrhage varies, but most episodes occur within two years of the initial observation. Of those cirrhotic patients who do bleed, 70% will die within one year of the first hemorrhage and 60% who have bled once will bleed again within a year.

The key factor that predisposes to bleeding of esophageal varices is probably related to the pressure across the venous wall. This pressure can be considered to be the algebraic sum of the pressures inside and outside the vein, considering the internal pressure as positive (because it contributes to bleeding) and the external pressure as negative (because it prevents bleeding). As the diaphragm descends in inspiration, the pressure in the abdomen increases and this pressure squeezes on all of the portal veins and forces blood under increased pressure into the chest. In the chest, the same force decreases the pressure on the outside of the vein. At the lower end of the esophagus the pressure in the vessels rises quickly, while the outside pressure decreases. Therefore, conditions are such that there is a maximum force exerted to tear the wall of the vein. In the abdomen, the pressure is increased both inside and outside so there is little change in pressure across the venous wall. This small change in pressure is thought to be the reason that bleeding usually occurs only in the lower end of the esophagus.

Although patients with varices have by definition collateral circulation, the portal pressure remains elevated because these collateral vessels are too small and are too tortuous to effectively lower the pressure.

Esophagitis also causes bleeding from varices in some patients. Inflammation and its associated edema make the tissues weak and more likely to bleed.

DIAGNOSIS OF ESOPHAGEAL VARICES

Endoscopy

Endoscopy is the quickest and safest method for determining if a patient has bleeding varices. /3/ In patients with a massive hemorrhage, it is impossible for the endoscopist to see the exact source of bleeding; in such patients angiography or a therapeutic trial with a Sengstaken-Blakemore (SB) tube is necessary. Investigators have proved that patients with cirrhosis and varices who develop gastrointestinal hemorrhage will bleed from a source other than the varices 50% to 60% of the time. Large tortuous esophageal varices are readily distinguishable by endoscopy as well as by x-ray /4/; however, smaller varices are difficult to detect. Observer error in diagnosing esophageal varices by endoscopy approaches 20%. The chief difficulty in most cases is that of distinguishing varices from mucosal folds. By observing the movement of the esophagus, one can often distinguish the mucosal folds because they relax and disappear during motility, whereas varices do not. The color of the varices and the serpiginous course that they usually take, can be quite helpful. DaGradi /5/ developed a scale for grading varices that corresponds to the longitudinal extent and the diameter of a varix. Grade 1 varices are 2 mm or less in diameter and grade 5 varices are large, grape-like clusters present or seen in the lumen of the esophagus. Palmer and Brick /6/ grade varices on a scale of mild to severe, the mild ones being less than 3 mm and the severe ones being over 6 mm in diameter. It is obviously difficult to achieve a grading system for the cases when a great many subjective decisions must be made. The color of varices as seen through the fiberoptic endoscope varies from blue to red, but one must not expect to see blue regardless of the size of the varix.

Various techniques including visualization through a piece of red plastic and balloon distention have been attempted in an effort to improve the endoscopic diagnosis of varices.

Boyce /7/ defines a varix as "any submucosal vein which, when viewed at a magnification of 4 mm in diameter, elevates the esophageal mucosa in a patient who is lying in a horizontal position and breathing quietly and easily." The distribution of varices is easily measured by the length of the esophagoscope.

One of the most important ways in which the endoscopist can aid the surgeon to treat a bleeding patient is to "clear" the esophagus, a source of upper gastrointestinal hemorrhage. If the esophagoscopist sees a clot on a varix, or actually sees a bleeding point on a varix, this finding is excellent evidence. However, if insertion of the endoscope into the stomach and duodenum indicates there is no bleeding in this area, but blood continually wells up into the esophagus as the instrument is withdrawn, the patient probably has variceal bleeding. In one study /8/ in which 16% of the patients were bleeding from varices, it was not possible to establish the bleeding point with certainty because of the massive amount of bleeding that continually welled up into the esophagoscope. Esophageal varices were seen to be bleeding in slightly more than 50% of the patients. Because the alcoholic patient with cirrhosis probably has upper gastrointestinal bleeding for reasons other than varices, it is also helpful if the endoscopist can find either another potential source or an actual source of bleeding in the stomach or duodenum.

Vascular Procedures

Splenic portal venogram. When radiopaque dye is injected into the spleen, a radiographic outline of the course of the contrast medium in the blood vessels which drain the spleen can be obtained. In a healthy person, only a single splenic vein draining into the portal vein should be seen. Splenoportography, a procedure seldom employed since the availability of arterial portography, is still useful following portacaval shunt to demonstrate the patency of the shunt. In this circumstance, no collateral circulation should be visible and there should be direct flow of the contrast medium from the portal vein into the vena cava.

Superior mesenteric artery injection. Contrast media can be directed into the splenic or superior mesenteric artery at a rate of 10 ccs per second and filming can be prolonged up to 25 seconds. This produces good views of the superior mesenteric and the splenic veins. /9/ Nebesar and Pollard /9/ emphasized that "arterial portography" is the diagnostic procedure of choice when the spleen has been removed or when splenoportography is contraindicated. This procedure is done to prove the patency of the portal vein, and to display the patency of a portacaval shunt after splenectomy.

The angiographer can usually obtain an extremely good demonstration of varices around the esophagus by injecting Hypaque into the left gastric artery.

Barium Swallow

The radiologist can demonstrate esophageal varices by barium swallow in less than three-fourths of the patients with proven esophageal varices. Varices are usually seen below the level of the aortic arch and can best be demonstrated with the patient in the right anterior oblique or the left anterior oblique position. Some radiologists prefer a Valsalva maneuver, while others insist that the patient perform a Mueller maneuver. Often, it takes longer to explain to a patient what a Mueller maneuver is than it does to perform an endoscopy. Conn, et al /11/ showed that there was a great variation among radiologists in their attempts to diagnose esophageal varices by barium swallow. In most cases, each radiologist disagreed with his previous interpretation one time out of five. Although the radiologist may demonstrate unequivocally the presence of esophageal varices, this does not give any evidence that the patient is bleeding from the varices. Only by direct visualization of the esophagus can this diagnosis be made.

TREATMENT OF BLEEDING VARICES

Supportive and Resuscitative Measures

In the patient with acute variceal hemorrhage, shock is often present and is the first priority for treatment. Fluids and fresh blood, if available, are infused. Nursing care must be of the highest quality. We prefer to pass a large-bore soft rubber tube into the stomach and begin

water or saline lavage as soon as possible. The lavage serves at least two purposes: to remove as many clots and as much blood from the stomach as possible to facilitate endoscopic examination and to effect, perhaps, some hemostasis. In those patients who show impending or frank hepatic coma, neomycin, 1 gram every four hours, is started or lactulose may be given either orally or in enema form. In these patients, analgesics and hypnotics should be avoided because of their compromised liver status. It is also important that overexpansion of the patient's blood volume be avoided because this may increase the propensity for varices to bleed.

Immediately after starting resuscitative measures, the physician must try to ascertain the site of the bleeding. When it has been established that varices are actually bleeding, it is usually advisable to give the patient 10 mg of vitamin K, intramuscularly. Currently, we give vasopressin to such patients in an attempt to stop their bleeding.

Vasopressin

Antidiuretic hormone (ADH) is available in two types of preparation: (1) an extract with no separation of the ADH and oxytocic principle; (2) vasopressin which is prepared from posterior pituitary glands of domestic animals by separation of ADH from oxytocic hormone or by synthesis. Activity is designated as pressor units and is determined by comparison with a United States Pharmacopeia (USP) standard. A vasopressin injection contains 20 pressor units and not more than one oxytocic unit per milliliter. When 20 units of the vasopressin per five minutes are infused intravenously into normal individuals or into patients with portal hypertension, there is a decrease in portal blood flow and pressure lasting about 30 minutes. The moderate rise in blood pressure is probably caused by the marked splanchic vasoconstriction. Vasopressin causes increased intestinal activity, defecation, and abdominal cramps. In fact, the patient who receives intravenous or intraarterial vasopressin should have markedly increased intestinal activity, and probably defecation, if the drug is active. If vasopressin is stored for long periods of time, it will become ineffective. Unfortunately, coronary circulation is also affected; the drug should not be given to patients with known arteriosclerotic cardiovascular disease.

Intraarterial Vasopressin

Intraarterial vasopressin has been effective in the treatment of massive upper gastrointestinal hemorrhage. /11/ Selective arterial angiography which can be used to diagnose the cause of bleeding in a patient with brisk hemorrhage also offers an opportunity for therapy because vasopressin can be infused into the superior mesenteric artery to effect hemostasis, for example, for variceal bleeding. In one study /8/, vasopressin infusion therapy was associated with hemostasis in five of nine patients bleeding from varices. In a prospective controlled clinical trial comparing conventional therapy with that of therapy plus intraarterial vasopressin, survival was not affected by the addition of vasopressin administration. Another recent study /10/ has shown that peripheral, intravenous infusion of vasopressin is probably just as effective in lowering portal pressure as intraarterial infusion.

Intravenous Vasopressin

In light of such studies, we now give the patient with bleeding esophageal varices an infusion of 20 units of vasopressin mixed with 200 ccs of 5% dextrose in water over a 20 to 30 minute period. If the bleeding does not cease, another infusion of similar amounts may be tried. If this is successful, a continuous infusion of a dose of vasopressin ranging from 0.1 unit per milliliter per minute to 0.3 units per milliliter per minute is administered for a prolonged period of time. A Holter Model 9-11 infusion pump is used.

Sengstaken-Blakemore Tube

If the above treatment regimen is unsuccessful, an SB tube is used in the effort to control the hemorrhage (Figure 2). Although some investigators have had discouraging results using the SB tube in variceal bleeding, others have achieved safe and effective hemostasis on an emergency basis. There are several important factors in using the tube that can spell success, failure, or even death, in a patient. A step-by-step procedure for using the SB tube is found in Appendix E.

The dangers of using the SB tube consist of aspiration, asphyxiation, and ulceration. It is worthwhile to remember that variceal bleeding occurring in patients with extrahepatic portal obstruction usually stops without the use of tamponade.

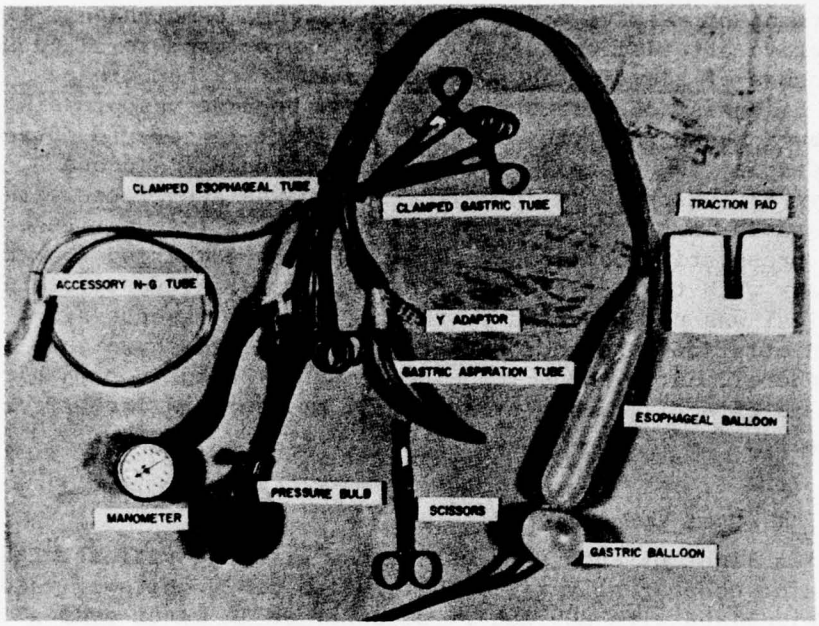

Figure 2. Boyce modification of the Sengstaken-Blakemore tube with basic accessories.

Sclerosing Agents

Esophageal varices may be obliterated by injecting them with a sclerosing solution through an endoscope. Formerly, this procedure was done through rigid instruments; however, with the advent of the long flexible needle that passes through the biopsy channel of a fiberoptic instrument, this procedure is now simpler and safer. Because successful variceal sclerosis within the esophagus increases the size and the pressure in gastric varices, the technique is ordinarily contraindicated when large gastric varices are present. The method requires a good deal of technical expertise and has not achieved wide popularity. The sclerosing agents which have been used include sodium morrhuate in 5% solution, Keflex®, and 50% glucose.

Transhepatic Obliteration of Varices

Recent studies were performed in which a patient with variceal bleeding underwent a procedure in which a

cholangiography needle was inserted into the liver and then advanced under fluoroscopy into the splenic pulp. From there the catheter was advanced over a guidewire as far as possible along the splenic vein. The major variceal supply veins, which include the left gastric and short gastric veins, were thrombosed using 500 units to 3,000 units of thrombin in 30 ccs of 50% dextrose. In one study, six of 13 decompensated cirrhotic patients with bleeding varices were successfully treated in this manner. Greater experience is necessary before the effectiveness of this procedure can be determined.

Laser Energy

The use of laser energy to control upper gastrointestinal hemorrhage is now possible. The work of Frühmorgen and Kiefhaber* and others has shown this to be an effective method of treatment in patients with bleeding lesions in the stomach, and in some cases, of variceal bleeding. Certain properties of the laser make it a desirable technique for treating bleeding lesions, e.g., noncontact with the tissue, maneuverability under direct vision, absence of electric current flow through body tissue, and the greater therapeutic spectrum with respect to electrocoagulation. We have had experience at Letterman Army Medical Center (LAMC) using an argon-ion laser beam to effect hemostasis in bleeding duodenal lesions in rhesus monkeys; however, a great deal of experimental work still must be done before this technique achieves widespread clinical usage. Of interest is the newer neodymimum-YAG laser that is being used in Europe, particularly for coagulation of bleeding esophageal varices. The depth of penetration of the laser in blood or tissue is five times greater with the neodymimum-YAG than with the argon-ion laser. This is because the argon beam is completely absorbed by a 0.2 mm film of blood whereas with the neodymimum-YAG beam, a film five times as thick, i.e., 1 mm, is needed for complete absorption. This effect is produced because with identical power transmission for each laser, the heat produced per unit volume of tissue by the argon is some five times greater. The power required with the neodymimum-YAG laser must be five times higher than with the Argon beam. Therefore, damage to deeper lying layers

* Personal communication.

of intestinal wall must be expected. Nevertheless, Frühmorgen has successfully treated patients with massive variceal bleeding with a YAG laser.

One of the most attractive features of this type of technique is that it combines a diagnostic technique and a treatment modality. This opens up an exciting field for endoscopists in treating patients with bleeding varices.

Surgical Methods

Shunts

Although the question regarding the best surgical procedure in portal systemic shunt surgery is not yet settled, it is generally agreed that the portacaval shunt is preferable because it is technically easier to perform and is more likely to remain patent. All portal systemic shunt operations can cause recurrent hepatic encephalopathy in some patients. There is an argument about the relative frequency of the complication, but 20% is probably a minimum. /12/ Unfortunately, no sure method is available to predict which patient will do poorly after a shunt is performed. Inability to predict encephalopathy and the lack of proof of increased longevity after an operation in three recently published controlled trials have done much to cool enthusiasm for shunting. Nevertheless, in patients with massive hemorrhages from esophageal varices, some type of shunt operation may be life-saving. Surgery is indicated in all patients with apparent extrahepatic block who have had bleeding esophageal varices; this procedure will probably prolong their life and prevent further bleeding. Obviously, if the portal vein is not patent it cannot be used. When it can be performed, a portacaval shunt is indicated.

Ligation of Varices

Depending upon the situation the surgeon encounters, surgical ligation of esophageal varices may be the only procedure that can be performed.

TREATMENT SUMMARY

In summary, the following procedures are currently used at LAMC for treating patients with massive bleeding from esophageal varices.

All patients with massive upper gastrointestinal hemorrhage are admitted to the Intensive Care Unit (ICU). After evaluation of the patient's condition and stabilization with blood transfusion and fluids, lavage is performed using iced water or saline. As soon as possible, an emergency fiberoptic endoscopy is performed. In most cases, no sedation whatsoever is used in these patients; however, in the rare patient in whom the procedure cannot be done and bleeding continues despite all efforts to control it, a diagnostic endoscopy can be performed in the operating room with the patient under general anesthesia with an endotracheal tube in place. This procedure is usually done prior to emergency surgery.

If esophagoscopy establishes that bleeding is from the varices, or if endoscopy does not reveal a bleeding site, but it is suspected that varices are the cause of hemorrhage, a therapeutic trial with the SB tube is instituted. In addition, the patient receives intravenous vasopression, as discussed above, provided there is no history of coronary artery disease. After bleeding is controlled and the diagnosis of bleeding esophageal varices is confirmed, the next step is to arrange for the appropriate surgical procedure.

If emergency surgery becomes necessary and it is not possible to perform a shunt, only transthoracoesophageal suture of bleeding varices can be performed. It must be emphasized, however, that this does not decompress the portal venous system which causes the varices, and secondary bleeding may be expected to occur several months postoperatively. For this reason, every effort should be made to improve the patient's general condition from a nutritional standpoint so that a definitive procedure of portal systemic shunt can be performed, preferably at the end of a six-week period.

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Shumway's Law: Bleeding always stops.

CONGENITAL HEPATIC FIBROSIS WITH SEPSIS AND HYPERSPLENISM

Major John Seaman, MC

Since its first pathologic description in 1856 /1/, approximately 150 cases of congenital hepatic fibrosis have been reported. In their classic 1961 review, Kerr et al /2/ applied the term "congenital hepatic fibrosis" to describe a distinct entity emphasizing normal lobules of liver parenchyma which are separated by wide bands of mature fibrous tissue and accompanied by interlobular bile ducts and hypoplastic portal veins. Because congenital hepatic fibrosis is frequently associated with cystic dilation of the intrahepatic biliary tree and renal dysplasia, a variety of clinical presentations are possible. Portal hypertension with upper gastrointestinal bleeding and hepatosplenomegaly is the most common presentation, accounting for more than 80% of cases. Renal disease, cholangitis, sepsis, or hypersplenism predominate the clinical picture less frequently.

In this paper, we report an unusual case of congenital hepatic fibrosis presenting with life-threatening cholangitis and sepsis, complicated by hypersplenism.

CASE REPORT

A previously healthy 22-year-old male was admitted to Letterman Army Medical Center (LAMC) with a three-day history of right upper quadrant pain, fever, stupor, leukopenia, and thrombocytopenia. Five days prior to admission, he consumed a moderate amount of beer and rum. Over the ensuing three days, he developed nausea, vomiting, loose stools, fever, and disorientation, and was admitted to Silas B. Hays Hospital, Fort Ord, where a temperature of 40° C (104° F), hepatosplenomegaly, and mild liver tenderness with slight scleral icterus were noted. Laboratory tests performed there showed a hematocrit of 42%, white blood cell count (WBC) of 1,900, 45 polymorphonuclear neutrophil leukocytes (PMN), 15% bands, 27% lymphocytes, 11 monocytes, two metamyelocytes, and a platelet count of 49,000/cu mm. Serum bilirubin was

3.5 mg/100 ml (1.6 mg/100 ml direct). Serum glutamic oxalocetic transaminase (SGOT) was 2½ times normal, and alkaline phosphatase was normal. Urinalysis revealed low grade glycosuria, proteinuria, hematuria, and pyuria. A bone marrow aspiration and biopsy revealed hypocellular elements with normal appearing elements. Blood cultures grew gram negative rods. The patient was placed on intravenous gentamycin and Velosef® . After two days, he was transferred to LAMC because of continued fever, thrombocytopenia, and leukopenia. There was no family history of hepatic or renal disease. Past medical history was unremarkable with no note of hepatic enlargement on induction physical, nor episodes of jaundice, fever, or gastrointestinal bleeding. The patient denied foreign travel except for an uneventful weekend trip to Tijuana, Mexico, 40 days prior to this admission. His alcohol consumption was limited to occasional weekend abuse for one year. There was no history of drug abuse.

Physical examination revealed a slender, confused, delusional young man with no signs of chronic liver disease. His temperature was 38.3° C (101° F). His abdomen was soft, flat, nontender, with a 20 cm firm, nontender liver and a palpable spleen tip. He had a soft apical systolic murmur without radiation. There was no evidence of congestive heart failure or peripheral emboli. His cornea were clear, and there was no lymphadenopathy. Except for moderate confusion and disorientation, the neurologic examination was unremarkable.

Laboratory data showed a hematocrit of 39%, WBC of 1300 46 neutrophils, 2% monocytes, 2% bands, 2% eosinophils, and 48% lymphocytes) and platelet count of 70,000/cu mm. His serum bilirubin was 3.3 mg/100 ml; SGOT and lactic dehydrogenase (LDH) were normal, with an alkaline phosphatase of 128 mU/ml (110 normal). Serum creatinine was 1.0 mg/100 mm and blood urea nitrogen (BUN) was 25 mg/100 ml. Prothrombin time (PT) and partial thromboplastin time (PTT) were normal. Coombs' test and disseminated intravascular coagulopathy (DIC) screens were negative. Electrocardiogram, chest x-ray, and cerebral spinal fluid examination were normal. Skin tests were nonreactive.

During his first two weeks at LAMC, the patient's course improved on parenteral antibiotics. A percutaneous

liver biopsy on the second hospital day returned several small fragments of liver tissue revealing parenchyma with a suggestion of periportal fibrosis and periportal infiltrate with PMNs. There was no bile stasis.

An abdominal ultrasound showed a 10 cm lucent gallbladder without stones or evidence of cystic structures involving liver. An oral cholecystogram returned a faintly visualizable gallbladder without evidence of stones. A gallium scan was normal. A repeat bone marrow revealed hyperplasia of all cell lines. An upper gastrointestinal series was also normal.

The patient's hematocrit stabilized at 37%. His WBC rose to 4,800, and his platelet count rose to 179,000/cu mm during this period, but by the second week it began to decline again. On the 20th hospital day, while off antibiotics, the patient became febrile, with tender liver and enlarging nontender spleen extending 12 cm below the costal margin. Although his fever responded promptly to antibiotics, his peripheral cell counts deteriorated. By hospital day 23 his WBC had fallen to 1,100 with 28% PMNs and his platelet count had fallen to 67,000/cu mm. His hematocrit was 30.4% without evidence of DIC, intravascular hemolysis, or blood loss.

Exploratory laparotomy and splenectomy were performed on the 23rd hospital day. At the time of operation, the liver appeared firm and large, and had the appearance of "nutmegging." There was no evidence of cystic disease, extrahepatic biliary dilation, or gallstones. The spleen was grossly enlarged and engorged in appearance.

Postoperatively, the expected rebound in platelet count and WBC occurred (800,000/cu mm and 20,000 respectively), with eventual normalization.

Pathologic sections of the spleen revealed fibrocongestion. Lymph nodes were normal. Wedge biopsy of the liver, however, contained striking periportal fibrosis, dilated proliferated biliary radicals lined with cuboidal epithelium, minimal infiltration with inflammatory cells, and normal hepatic parenchyma (see figure).

Figure. Intraoperative wedge biopsy of a case of congenital hepatic fibrosis demonstrating striking fibrosis, bile duct dilation and proliferation, and normal parenchyma.

The postoperative course was unremarkable. A renal scan revealed bilaterally enlarged cystic kidneys, and an intravenous pyelogram displayed calyceal ectasia and medullary sponge kidney. Endoscopy showed dilatation of gastric veins consistent with portal hypertension. A computerized axial tomogram of the liver demonstrated the 10 cm gallbladder but failed to reveal intrahepatic cysts.

DISCUSSION

The inherited nature of congenital hepatic fibrosis is not disputed by most authors. However, only half of the cases reported involve an affected sibling. /3,4/ The remaining cases appear sporadically. Incidence among males and females is approximately equal. Interestingly, no cases of congenital hepatic fibrosis in successive generations have been reported. Controversy continues concerning the precise mode of transmission of the disease. The basis for this controversy revolves around its variable association with polycystic renal disease and other organ dysplasia. Blyth and Ockenden /5/ present arguments for dividing the disease (which they refer to as "polycystic disease of kidney and liver") into four groups, each determined by a mutant gene and distinguished by the relative severity of the renal and hepatic lesions. If the renal disease predominates, the patient dies in infancy of uremia, with minimal hepatic fibrosis. The less renal impairment present, the longer the patient survives, and the more prominent the liver involvement becomes. Whether this represents development of hepatic fibrosis with time is not known.

Other types of renal involvement are also associated with congenital hepatic fibrosis; these vary from infantile or adult polycystic kidney disease /6/ and medullary sponge kidney to glomerular and proximal tubular fibrosis. /7/ Structural renal disease, often in the form of medullary sponge change, is reported in approximately 80% of cases, but renal impairment is rarely significant. /8/

Another abnormality frequently associated with congenital hepatic fibrosis is cystic dilation of the intra- and extrahepatic biliary tree, which in its pure form occurs without fibrosis and is termed "Caroli's disease." In

contrast to the hepatic cysts of cystic renal disease, which do not communicate with the biliary tree, the cysts of Caroli's disease are an extension of dilated intrahepatic biliary ducts. Occasionally isolated to a single lobe, these cystic deformities predispose the patient to intrahepatic gallstones and recurrent cholangitis. This abnormality is best demonstrated by intraoperative T-tube cholangiography but occasionally may be seen by intravenous cholangiography and sonography. Percutaneous and endoscopic retrograde cholangiography is felt to be contraindicated because of the threat of inducing infection. The use of computerized axial tomography to demonstrate dilated intrahepatic ducts of Caroli's disease, although not reported, is an attractive alternative to more invasive procedures.

Other congenital abnormalities involving the pancreas, lungs, and brain (Meckel's syndrome) are seldom associated with the pathologic findings of the liver identical to congenital hepatic fibrosis.

Portal hypertension develops in 75% to 90% of cases of congenital hepatic fibrosis; variceal bleeding occurs in two-thirds of these cases. Elevated portal pressures are attributed to the hypoplastic portal venous system which gives rise to a presinusoidal block. Ascites, therefore, is a rare finding in congenital hepatic fibrosis. Despite the frequent occurrence of splenomegaly, hypersplenism is rarely encountered. In Kerr's review /2/, no patient with congenital hepatic fibrosis had a significantly decreased WBC, and three of 13 patients had platelet counts less than 100,000/cu mm. Lieberman /3/, likewise, reported only one patient in 47 with a decreased platelet count. Hermann and Hawk /9/ reported a case of upper gastrointestinal bleeding and hypersplenism in a 14-year-old boy. In that report, they stated that once splenectomy has been performed, portal decompression procedures for portal hypertension may safely be delayed until gastrointestinal bleeding occurs. That such procedures can give prolonged survival in patients with congenital hepatic fibrosis is related to their comparatively normal liver function.

The laboratory findings in cases of congenital hepatic fibrosis rarely reveal significant hepatic or renal impairment. Alkaline phosphatase may be slightly elevated and

temporary elevation of bilirubin, SGOT, alkaline phosphatase, and WBC may occur with cholangitis. Occurrence of mild pyuria and pyelonephritis are not uncommon.

The diagnosis of congenital hepatic fibrosis is almost invariably delayed until surgery, when an adequate biopsy of the liver can be obtained. Percutaneous liver biopsy usually returns only a few fragments of tissue. Frequently, it does not contain enough portal area for the diagnosis to be made. On the other hand, if portal hypertension occurs in a child, the diagnosis can tentatively be made by finding intrahepatic portal venous hypoplasia with a normal wedge pressure by splenoportography and celiacoportography.

The prognosis is generally less favorable in those individuals who develop recurrent cholangitis. Although gallstones frequently occur in patients with accompanying "Caroli's disease", cholecystectomy has not been shown to decrease the frequency of biliary tract infections. Left lobe hepatectomy was reported as successful in resolving recurrent cholangitis in one patient with involvement limited to that lobe. In most patients, however, dilation of the biliary tree is too widespread for this approach to be taken. Surgical drainage of the common bile duct through an external T-tube or choledochoduodenostomy in an effort to reduce bile stasis and stone formation has generally met with little success. Prophylactic antibiotics have been used to reduce the recurrence of cholangitis; however, success with this mode of therapy is not well documented.

CONCLUSION

Congenital hepatic fibrosis may present with any combination of events, including cholangitis, renal disease, upper gastrointestinal bleeding, or hypersplenism. Generally, it occurs in the setting of hepatosplenomegaly and relative normal liver function tests in young individuals. Definite diagnosis is usually delayed until laparotomy has been performed.

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Under carefully controlled conditions,
machines and organisms behave as they please.

APPENDIX A

THERAPY OF ASCITES SECONDARY TO LIVER DISEASE

Lieutenant Colonel David C. Staples, MC

TREATMENT SUMMARY

1. Make a definitive diagnosis with paracentesis (usually transudative ascitic fluid).
2. Obtain baseline serum and urine electrolytes, blood urea nitrogen, creatinine and weight.
3. Monitor daily weights and intake and output.
4. Attempt to diurese the patient:
   a. One-half pound per day for patients with peripheral edema
   b. One-half to one pound per day for patients without peripheral edema
5. Maintain bed rest.
6. Restrict sodium (500 mg sodium per 24 hours).
7. Restrict fluids only if serum sodium is less than 130 mg% (1,000 to 1,500 cc per day).
8. If after four days weight loss is less than four pounds:
   a. Add Aldactone® 25 mg every six hours (allow two to five days for maximum effect).
   b. If unresponsive, add Thiazide® diuretics (50 to 100 mg Hydrochlorothiazide® per day).
   c. If unresponsive, increase Aldactone® to 200 to 300 mg per day.
   d. Monitor for azotemia, electrolyte imbalance, and encephalopathy.
   e. If still unresponsive, consider ascitic fluid reinfusion combined with Lasix® or a LaVeen shunt.

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THERAPY OF THE HEPATORENAL SYNDROME

TREATMENT SUMMARY

1. **Establish a presumptive diagnosis with appropriate clinical and biochemical features.**

   a. Clinical features

      (1) Severe hepatic failure

      (2) Ascites

      (3) Oliguria

   b. Biochemical features

      (1) Hyponatremia

      (2) Progressive azotemia with blood urea nitrogen/creatinine ratio greater than 10

      (3) Urine specific gravity greater than 1.010

      (4) Urine sodium less than 10 milliequivalents per day

2. **Rule out prerenal azotemia with fluid challenge.**

3. **General supportive care:**

   a. Maintenance of fluid and electrolyte balance

   b. Treatment of ascites and encephalopathy

4. **Consider:**

   a. Ascitic fluid reinfusion

   b. Use of pharmacologic agents

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APPENDIX B

HEPATIC ENCEPHALOPATHY

Major John A. Dale, MC

TREATMENT SUMMARY

1. Evaluate history and perform physical examination carefully to determine etiology of hepatic failure (acute versus chronic disease). If etiology is chronic, search for precipitating factors. Give special attention to gastrointestinal (GI) bleeding, infection, electrolyte imbalance, and sedative and hypnotic agents.

2. Establish stage of coma (Table in text).

3. Correct precipitating factors as much as possible.

4. Prescribe a protein-restricted diet with supplemental calories provided by fats and carbohydrates via intravenous or nasogastric hyperalimentation, as necessary.

5. Monitor complete intake and output.

6. Monitor mental status daily.

7. Weigh patient daily.

8. Evaluate patient for development of aggravating factors. Give special attention to GI bleeding, infection, electrolyte imbalance, and sedative and hypnotic agents.

9. Take complete blood count, prothrombin time, partial thromboplastin time, and platelet count daily.

10. Check all stool for occult blood.

11. Determine serum and urine electrolyte levels daily.

12. If ascites is present, perform paracentesis initially to find etiology and later to search for peritonitis whenever fever develops.

13. Obtain biweekly liver function tests.

14. Monitor blood glucose in fulminant disease carefully.

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15. Measure blood urea nitrogen and creatinine daily to monitor for hepatorenal problems.

16. Decrease nitrogenous absorption with lactulose or neomycin.

17. Treat coagulation deficiencies as necessary.

18. Replace vitamin deficiencies as needed, e.g., folate, thiamine, and vitamin K.

19. Use endotracheal intubation and respiratory support as indicated by stage of coma.

APPENDIX C

COAGULATION ABNORMALITIES

Major Richard W. Houston, MC

TREATMENT SUMMARY

1. **Abnormal clotting studies without clinically significant bleeding**
   a. Give trial of AquaMephyton®
   b. Give antacid therapy, 1 and 3 hours after meals and at bedtime or give Cimetidine®, 300 mg four times a day with meals and at bedtime
   c. Avoid unnecessary needle sticks, potentially ulcerogenic medications, and medications interfering with platelet activity
   d. Perform stool guaiacs and observe patient closely for signs of bleeding
2. **Abnormal clotting studies with clinically significant bleeding**
   a. Prolonged prothrombin time (PT) and partial thromboplastin time (PTT)
      (1) Give trial of AquaMephyton®
      (2) Give fresh frozen plasma, fresh whole blood, or clotting factor concentrates as needed
      (3) Check fibrinogen level and platelet count
   b. Thrombocytopenia
      (1) Give platelet transfusion as needed if thrombocytopenia is a significant factor in bleeding
      (2) If prolonged PT and PTT with low fibrinogen, obtain hematology consult for disseminated intravascular coagulation (DIC) screen)
      (3) If coagulation studies are suggestive of DIC and hemorrhage is severe enough that heparin therapy is being considered (rarely indicated), obtain factor VIII level.

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c. Normal platelet count.

(1) If prolonged prothrombin time and partial thromboplastin time with low fibrinogen, obtain euglobulin lysis time and hematology consult.

(2) If coagulation studies are suggestive of primary fibrinolysis and hemorrhage is severe enough that Amicar® therapy is being considered (rarely indicated), obtain factor VIII level.

3. Additional considerations

a. Rule out correctable sources of bleeding.

(1) Use endoscopy if upper GI bleeding is present.

(2) Use proctoscopy and further workup as appropriate for lower GI bleeding.

(3) Emphasize good oral hygiene.

(4) Discontinue medications which could possibly contribute to bleeding problems.

b. Heparin or Amicar® therapy should not be considered without hematology consult.

c. Always consider the limitations of the blood bank when ordering blood or blood components. Reevaluate therapy daily to avoid abuse of blood bank.

APPENDIX D

FULMINANT HEPATIC FAILURE

Major John J. Jolley, MC

THERAPEUTIC GUIDELINES

1. **Neurologic alterations**
   - a. Hepatic coma
     - (1) Withdraw all oral protein
     - (2) Cleanse protein from gut with lactulose
     - (3) Administer neomycin enema
     - (4) Give oral neomycin, 500 mg four times a day
     - (5) Give lactulose, 30 cc every other hour until watery diarrhea starts, then decrease till three to five soft stools develop
     - (6) Avoid use of sedatives
   - b. Vasomotor collapse
     - (l) Rule out sepsis, bleeding
     - (2) Replace fluid with central monitoring
     - (3) Use vasopressors as needed
   - c. Respiratory failure
     - (l) Perform prophylactic tracheostomy, Stage III
     - (2) Monitor arterial blood gases
   - d. Cerebral edema
     - (l) Restrict fluids
     - (2) Avoid hypotonic fluids
     - (3) Avoid corticosteroids
     - (4) Obtain neurologic consultation
2. **Metabolic disorders**
   - a. Hypoglycemia

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(1) Monitor blood sugar every four hours

(2) Infuse glucose. (Kilogram quantities per day may be required.

b. Renal failure

(1) Attempt fluid challenge

(2) Rule out acute tubular necrosis

(3) Avoid use of diuretics

(4) Use early dialysis

c. Electrolytes

(1) Monitor daily

(2) Obtain blood gas daily

3. Bleeding

a. Gastrointestinal

(1) Administer Cimetidine, 300 mg intravenously every six hours (prophylaxis)

(2) Do stool guaiac frequently

(3) Obtain hematocrit frequently

b. Hemostasis

(1) Administer vitamin K

(2) Administer fresh frozen plasma, 15 cc to 20 cc per kilogram, follow with one-third original dose every eight hours as needed to control bleeding

(3) Administer platelets as needed

(4) Obtain baseline disseminated intravascular coagulation screen

4. Infection

a. Do not use prophylactic antibiotics

b. Evaluate sputum and urine daily

APPENDIX E

CORRECT METHOD OF USING THE MODIFIED SENGSTAKEN-BLAKEMORE TUBE

Lieutenant Colonel Melvin L. Butler, MC

1. Make accurate diagnosis with endoscopy to assure that the acute bleeding is from a tamponable lesion.
2. Use a *new* Davol 20 Fr. Sengstaken-Blakemore (SB) tube with Boyce modification ("Accessory nasogastric (NG) tube") attached. Always check balloons under water just before use to assure there are no leaks.
3. Assure that the stomach and esophagus are reasonably empty. Use an Ewald tube.
4. Lubricate the modified SB tube, attach the "accessory NG tube" to constant suction, and then pass the SB tube through the *mouth* until the gastric balloon is well within the stomach.
   a. Tubes are easiest to introduce with the patient in the left lateral decubitus position.
   b. A guide wire or flexible wand in the gastric tube lumen may ease tube insertion. Introduce it as if inserting a gastroscope.
5. Flush the gastric tube with 25 ml to 50 ml of air while auscultating over the epigastric area. Assure that the gastric tube is in the stomach, and not in the esophagus, before attempting step 6.
6. Inflate the gastric balloon with 250 ml to 275 ml of air while auscultating over the epigastric area. Stop immediately if the patient complains of sudden substernal pain or insufflation of air is not audible in the epigastric area.
7. Double clamp the gastric balloon inlet with rubber-shod surgical clamps.
8. Apply firm traction at the mouth of the tube so that the gastric balloon is firmly pressed against the diaphragm at the cardia.
9. Connect the gastric tube to intermittent suction.
10. Position keyholed traction pad at a corner of the mouth and tape SB tube securely to the pad. In dentulous patients, a plastic mouthpiece (Olympus Corporation of America) should be added around the SB tube.

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11. Inflate esophageal balloon to 25 mm to 45 mm of Hg pressure. Use the lowest pressure required to stop bleeding. *Do not exceed 45 mm of Hg pressure.*

12. Double clamp the esophageal balloon inlet with rubber-shod surgical clamps.

13. Switch "accessory NG tube" suction from constant to low intermittent suction and tape shut the connections on this system to prevent inadvertent lavage.

14. Maintain elevation of head of the bed on 6 inch to 8 inch blocks.

15. Tape scissors to the head of the bed within the clear view and quick reach of attendants.

16. Reinstruct all aides, nurses, interns, residents, and others who will be attending the patient.

17. Irrigate gastric tube approximately every ½ hour, and record the appearance of return.

18. Recheck and readjust tube traction and esophageal balloon pressure every 2 hours (inform physician only).

19. Make sure that an informed, trained attendant is at or near the bedside of the patient at *all* times.

20. Keep patient from taking anything orally and so advise *all* visitors. Once bleeding is stopped, certain necessary medications, i.e., neomycin, may be crushed and given in small volume via the gastric tube.

21. Assure proper oral hygiene, frequent deep breathing or coughing, and changing of body position.

22. Continue tamponade for 24 to 48 hours.

23. Deflate esophageal balloon only and relax traction on gastric balloon. Leave the gastric balloon inflated. This is best done at a time of day when close observation for rebleeding is assured.

24. Observe for rebleeding with tube in place another 12 to 24 hours.

25. If no rebleeding during the 12 to 24 hours occurs, pull SB tube out *after* complete transection of the tube with scissors to assure that tube is not reused and balloon is deflated before removal.

26. Begin appropriate liquid diet and use therapeutic amounts of a liquid antacid mixed with bismuth subcarbonate powder.

27. Should rebleeding occur while the tube is in place (as described in step 24) or after the tube is removed (as described in step 25), resume tamponade for another full course or as a temporary measure until emergency surgery is initiated.

28. From the time of tube insertion (step 4) until tube removal (step 25), continually reevaluate what the next course of action will be should tamponade fail or bleeding reoccur.

SENGSTAKEN-BLAKEMORE TUBE TRAY

1 – *New* Davol Sengstaken-Blakemore (SB) tube, 20 French. *(Never re-use SB tubes).*
1 – Plastic 18 French nasogastric (NG) tube sutured in place above the esophageal balloon with 2-0 or 3-0 black silk. Tip of NG tube must be at top of SB esophageal balloon.
1 – Aneroid blood pressure manometer
1 – Air bulb from blood pressure cuff
1 – Padded, key-holed mouth traction pad
5 – Rubber-shod surgical clamps (Kelly)
2 – Plastic Y connectors (1-5/16 inch or 3/8 inch in diameter, 1 inch to ¼ inch in diameter)
2 – Plastic straight connectors (2 ¼ inches in diameter)
1 – Pair surgical scissors
2 – 50 ml plastic syringes (bladder irrigation syringes)
3 – Large safety pins
3 – 6 inch lengths of rubber tubing – 3/8 inch outside diameter and 3/16 inch inside diameter
1 – Olympus mouthpiece

OTHER EQUIPMENT

2 – GOMCO suction machines *or* 1 GOMCO suction machine plus 1 wall suction
1 – Tube water-soluble lubricant jelly (K-Y)
1 – Roll of 3-inch tape

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The Golden Rule of Academic Advancement:

Do unto others as they would do unto you, only do it first.

●●●●●●●●●●●●

Furthermore:

A. Common things occur commonly.

B. The race may not always be to the swift nor the battle to the strong, but it's a good idea to bet that way.

C. When you hear hoofbeats think of horses, not zebras.

D. Place your bets on uncommon manifestations of common conditions rather than common manifestations of uncommon conditions.

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William Dock, M.D., on the use of penicillin to treat acute bacterial endocarditis in a patient with penicillin allergy: "Better red than dead."

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All rules and principles (except for Osler's Rules, Butler's Rule, Eric's Dictum, and Jolley's Dictum) are taken from Strauss MB: Familiar Medical Quotations. Boston, Little Brown and Co., 1968.

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